THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MARCH, 1960

ORIGINAL ARTICLES

STEROID-INDUCED ADRENAL INSUFFICIENCY AGGRAVATED BY SEVERE MEDICAL ILLNESS

By Robert S. Capper, Captain, MC
RESIDENT, DEPARTMENT OF MEDICINE, BROOKE ARMY HOSPITAL
BROOKE ARMY MEDICAL CENTER, FORT SAM HOUSTON, TEXAS

AND

Robert H. Moser, Major, MC
ASSISTANT CHIEF, DEPARTMENT OF MEDICINE, BROOKE ARMY HOSPITAL
BROOKE ARMY MEDICAL CENTER, FORT SAM HOUSTON, TEXAS

The meteoric rise to prominence of adrenocorticotropin and the adrenal cortical hormones as therapeutic agents has elicited an ambivalent reaction. The often incomprehensible and "magical" benefit derived from steroid hormones in many diverse and unrelated diseases has created an aura of mysticism surrounding these drugs that is unlike any previous experience in the annals of therapeutics. This has resulted in a situation in which these powerful agents have been employed as "trial of therapy" in a vast multitude of disease states in which conventional methods of therapy have been unrewarding. It is in this confused therapeutic milieu that we have observed the emergence of an entirely new spectrum of disease: "states induced by steroid therapy" (Allanby[2], Moser[39]). Many of these entities are well known to physicians and are properly respected. It is the purpose of this communication to focus upon one of the more subtle and devastating of these reactions (Adams and Siderius[1], Nicholas, Wilson and Umberger[40], Salassa *et al.*[46,47], Slaney and Brooke[51]). We will present 4 case histories to dramatize the phenomenon of Addisonian crisis arising to complicate a severe medical illness in patients treated in the past with steroids. In each instance the patient was either too ill to give an adequate history or was not aware of the nature of the medication previously administered. Each patient was in the throes of continuing and distressing decline despite apparently adequate therapy, until the underlying situation was appreciated and exogenous steroids were administered. Response was abrupt and sustained in every case. Comment on the individual cases will be presented following each presentation.

Case Reports. CASE 1. This 72-year-old Caucasian woman entered Brooke Army Hospital in April, 1958, with the chief complaint

of "swelling of her eyes and abdomen" for about one month.

The present illness began "several" years ago when she was advised that she suffered from hypothyroidism. Therapy was initiated with desiccated thyroid ("1 to 3 grains" per day). She remained on this medication until 2 years prior to admission, when she voluntarily discontinued therapy due to her sense of wellbeing. In this 2-year period the patient noted gradual deepening of her voice and progressive integumental changes (dryness of skin and fingernail brittleness). She observed mild dysphagia, decreasing tolerance to cold, fatigue, exertional dyspnea and constipation. She denied nausea, vomiting, abdominal pain or food intolerance. One month prior to admission the patient developed intermittent abdominal distention. Shortly thereafter bilateral periorbital edema appeared which persisted up to the time of admission.

The past medical history and family history added only that the patient had been under intermittent therapy of unknown type for an ill-defined arthritis until 3 years prior to admission. She had remained asymptomatic since that time.

Physical examination on admission revealed a 5′ 3″, 120-pound woman with remarkably coarse hair, thick dry skin of poor turgor, and notable periorbital edema. During the interview it was apparent that her voice was distinctly husky and she spoke slowly with mild slurring. Pulse rate was 72 and blood pressure 190/100. The thyroid gland was not palpable. Lung auscultation disclosed bilateral basilar rales. The left border of cardiac dullness was at the anterior axillary line; P2 was louder than A2. Her neck veins were distended at 30° elevation. There were no palpable organs or masses in the abdomen, but shifting dullness was demonstrated in the flanks. Rectal examination revealed internal and external hemorrhoids with some prolapse of rectal mucosa. Lower extremities were distended with non-pitting edema. Neurologic examination demonstrated sluggish reflexes in all areas.

Laboratory findings: Hemogram revealed a leukocyte count of 5,400 with normal differential distribution; hemoglobin was 9.6 gm. and hematocrit 31%. The total protein was 7.5 gm. % (albumin 4.2 gm. and globulin 3.3 gm.). Blood urea nitrogen was 18 mg. per 100 ml.; serum sodium 136 mEq. per L.; potassium 3.5 mEq. per L.; chlorides 94 mEq. per L.; CO_2 26 mEq. per L. Serology was negative. Serum cholesterol was 425 mg. per 100 ml.; alkaline phosphatase 2.9 K-A units. Chest roentgenogram demonstrated a cardiothoracic ratio of 20:28; a minimal amount of fluid obscured the left costophrenic angle. Cardiac fluoroscopy confirmed the cardiomegaly; no cardiac pulsations were visible (suggesting pericardial effusion). Electrocardiogram demonstrated low voltage throughout, prolonged QT interval and T wave lowering in the limb leads with inversion in V_2 through V_6.

A presumptive diagnosis of myxedema was entertained. This was confirmed by very depressed radioactive iodine uptake studies and PBI of 1.2 μg. per 100 ml. The patient was started on ¼ grain doses of desiccated thyroid and began a slow period of improvement. In late April she slipped while in the bathroom and fell heavily, sustaining a scalp laceration which did not penetrate the galea. However, bleeding was rather profuse, and she required one unit of blood as the wound was sutured. About 6 hours later the patient suddenly lapsed into profound shock. She was given additional blood and norepinephrine (in an intravenous infusion) with mild improvement. However, 12 hours after the onset of injury, her blood pressure fell to 90/50 despite all measures. The patient was cold and sweating. Electrocardiogram remained unchanged but for tachycardia. As a desperation measure, 100 mg. of hydrocortisone was added to the intravenous infusion. Within 5 minutes her blood pressure climbed to 125/90. Shortly thereafter it stabilized at 140/70. She continued to do well and was maintained on Solu-Cortef (100 mg. q. 8 hr., intramuscularly) for 2 days, whereupon it was gradually decreased. Her blood pressure remained stable over the next 2 weeks, but she was observed to become more lethargic. Prednisone was reinstituted at a dose of 10 mg. t.i.d., but her stupor continued. At this time her serum sodium was 125 mEq. per L., potassium 4.4 mEq. per L., chlorides 100 mEq. per L. and CO_2 23 mEq. per L. She continued to deteriorate slowly and hyponatremia progressed to 119 despite increased sodium feeding. Urinary sodium remained elevated despite the hyponatremia and both salt and steroids were increased. During this time the members of the family had been interrogated in detail. It was determined that the patient had been given cortisone therapy 3 years previously for treatment of her arthritis. She had taken this (in unrecalled quantities) for about 6 months. On her new regimen of increased salt, prednisone and desiccated thyroid, her clinical condition slowly improved. She was gradually weaned off steroids after about 3

weeks and maintained on NaCl tablets. Cardiac size decreased commensurate with improvement in her thyroid function. She was discharged from the hospital in June, 1958, to be followed as an outpatient.

COMMENT. This patient sustained an episode of minor trauma to her head, which was complicated by severe unrelenting hypotension. It is probable that the stress of the injury was greatly exaggerated by the basic clinical disease (severe myxedema) plus the unknown "steroid-induced adrenal insufficiency." We cannot rule out a spontaneous, albeit subclinical Addison's disease occurring simultaneously with the myxedema, or as a part of a partial panhypopituitarism. However, there were no Addisonian stigmata, and her ability to function without supportive steroids after the critical episode all suggest a subclinical adrenal insufficiency created or abetted by steroid therapy.

CASE 2. This 75-year-old white woman was admitted to Brooke Army Hospital in July, 1957. She entered with the chief complaint of abdominal pain.

Her present illness began 24 hours prior to admission. Two hours following a rather large dinner she had been seized with cramping, generalized abdominal pain which radiated to the back. The pain persisted and she was unable to sleep. On the day of admission she began to vomit and developed fever. The pain became more severe, localized to the right upper quadrant and radiated around and through to the back.

Past history was pertinent only in that she had undergone an uneventful cholecystectomy 10 years previously. In addition she had received therapy of unknown type for arthritis in the past.

Physical examination revealed an acutely ill, obese, white woman in severe distress, complaining of severe abdominal pain and nausea. Her pulse was irregular at about 110 per minute; blood pressure was 160/90; temperature 103° F. The remaining pertinent findings were confined to her abdomen. There was severe, generalized distention with a thick panniculus. Tenderness and guarding were marked over the entire upper abdomen. Bowel sounds were of fair quality with no peristaltic rushes. Rectal examination revealed only soft feces. Neurologic examination disclosed hyperactive deep tendon reflexes throughout.

Admission laboratory data revealed a leukocytosis of 21,800 with 95% neutrophils, 4% lymphocytes and 1% eosinophils. Hemoglobin was 11.5 gm.%, hematocrit 34%, and sedimentation rate 39 mm. per hour. Urinalysis yielded a specific gravity of 1.017, albumin 2+, with sediment demonstrating an occasional leukocyte and occasional granular casts. Serum amylase was 8,000 units. Abdominal radiographs were interpreted as negative for pancreatic lithiasis. Chest roentgenogram revealed old pleural calcification.

Soon after admission she was given 100 mg. of meperidine intravenously and nasogastric suction was instituted. She was given atropine (subcutaneously), and an intravenous saline infusion was started. The patient responded well and fell asleep. On the second hospital day the patient appeared quite pale. Her pulse and respirations were rapid, and the blood pressure had fallen to 80/50. She was unable to cerebrate adequately and could not communicate. An electrocardiogram revealed only a sinus tachycardia. Recalling the previous patient, the ward officers elected to try steroids prior to the institution of vasopressor therapy. She was given 200 mg. of hydrocortisone and 120 mg. of ACTH intravenously. Within 15 minutes her blood pressure had risen to 100/80, she became more alert and could communicate. She was continued on intravenous and oral steroid therapy for another 10 days as her pancreatitis subsided. On the following day it was learned from the patient's family that she had taken prednisolone in doses of 5 mg. per day for about a 6-month period several months prior to arriving in this area. Apparently this had been administered for her arthritis, but she had not been informed of the nature of the medication. The patient gradually recovered from her attack of pancreatitis and was discharged from the hospital without steroid therapy. She was advised about her adrenal status and given a "steroid wallet card."

COMMENT. This patient experienced a classic episode of acute interstitial pancreatitis and demonstrated an adequate initial response to standard therapy. However, she lapsed into sudden unremitting deterioration until exogenous corticoids were administered.

Apparently she had sufficient adrenal reserve to contain the minor stresses of routine daily life. The added stress of a significant medical illness supervened and overtaxed her adrenal capacity. The possibility of a spontaneous Addison's disease occurring fortuitously cannot be excluded. However, the absence of stigmata, the history of steroid ingestion and the clinical course, all militate against this possibility.

CASE 3. This 81-year-old man was admitted to Brooke Army Hospital in late August, 1956. On the morning of admission the patient had developed progressive abdominal pain and weakness of the legs. During the next hour his speech became slurred and he lapsed into semicoma with incontinence of urine. At the time of admission he was comatose with a temperature of 106°. Interrogation of the family disclosed that the patient had sustained several minor strokes during the 6-year period prior to admission.

Physical examination disclosed a thin, elderly, white man who was comatose and pale, but without evidence of cyanosis. Blood pressure was 70/0. His features were symmetrical but mouth and eyes were tightly closed. On forcing open the eyelids the eyes were observed to be deviated to the right and upward. The pupils were equal and reacted to light. Funduscopic examination could not be accomplished at this time. A 2-plus nuchal rigidity was present. His lungs were clear to percussion and auscultation and the heart revealed regular rhythm and an apical rate of 84. There was a grade II systolic blowing murmur over the entire precordium. Neurological examination demonstrated the deviation of the eyes to the right, but the remainder of the cranial nerves appeared to be intact. Despite his comatose state, he responded to forced flexion of the neck by grimace and groan but did not react to other painful stimuli. His extremities were flaccid with absent deep tendon reflexes in the lower extremities, but they were 2+ in the upper extremities. Superficial reflexes were absent, but no abnormal reflexes could be elicited.

Admission laboratory data disclosed a leukocytosis of 27,000 with 96% polymorphonuclears and 4 lymphocytes. Hemoglobin was 14.8 gm.%, hematocrit 46%. Fasting blood sugar 171 mg. per 100 ml., CO_2 20 mEq. per L., chlorides 109 mEq. per L., sodium 136 mEq. per L., potassium 4.2 mEq. per L., and BUN 17 mg. per 100 ml. Urine sediment (Sternheimer-Malbin stain) demonstrated innumerable red and white blood cells. Serology was negative. Spinal fluid contained 1,910 red cells per ml., protein 37 mg. per 100 ml. glucose 96.0 mg. per 100 ml., globulin and serology were negative.

The hospital course was characterized by unrelenting coma and shock. Continuous nasogastric suction and norepinephrine by intravenous drip were initiated immediately, as were rectal acetylsalicylic acid, penicillin and streptomycin following blood culture. During the first 48 hours his urinary output steadily declined, and despite continuous rapid norepinephrine infusion his blood pressure fell. His temperature during this period became normal, but the white blood count rose to 31,550 with marked shift to the left. Intense toxic granulation appeared in the leukocytes.

On the morning of the third day his urinary output was zero, pulse was weak and blood pressure was unobtainable. At this time hydrocortisone (200 mg.) was introduced into the intravenous infusion. Within one hour the patient was normotensive and the norepinephrine was discontinued. He was given 100 mg. of Solu-Cortef in the next intravenous infusion and subsequently was maintained on oral prednisone (10 mg., t.i.d.). After 7 days, steroid dosage was tapered and discontinued. The patient remained alert and no evidence of neurologic deficit could be demonstrated other than the sequelae of his prior cerebral vascular accidents. On questioning he recalled that he had been given "some kind of pills" for arthritis about 7 months prior to admission. He related that he had taken "20 tablets all told," and they had afforded him temporary relief of his joint pain.

On the seventh hospital day he was asymptomatic and was discharged to the care of his family. They were all instructed regarding the significance of his adrenal problem, and he was given a "steroid wallet card."

COMMENT. This elderly gentleman demonstrated very poor capacity to respond to the stress of his apparent cerebrovascular incident. A specific etiology could not be determined, but it was suggestive of a decrease in cardiac output associated with cerebral arteriosclerosis. The history of prior steroid ingestion, unresponsiveness of his vascular system to vasopressors and

dramatic reaction to adrenal cortical hormone therapy all suggested poor adrenal reserve. He was quite able to endure the minor stresses of daily life in a state of subclinical adrenal insufficiency without emergence of any Addisonian stigmata. However, he was unable to cope with the medical stress of the cerebral "accident." Again, spontaneous adrenal depletion cannot be excluded, but this would seem highly unlikely.

CASE 4. This patient was a 75-year-old retired Medical Officer admitted to Brooke Army Hospital on 3 June 1957 with a history of intermittent asthmatic attacks. On the day prior to admission he had undergone urethral catheterization and dilatation with a Foley catheter being left in place. Since that time he had periods of confusion and incoherence.

Past medical history revealed he had received many forms of antiasthmatic therapy in the past, but due to his confused state was incapable of defining what the medications had been. He had been engaged in the active practice of medicine up until the day of admission, representing a 15-year span since his retirement from the US Army in 1942. He had always considered himself to be in fairly good health but for bronchial asthma and probable emphysema.

On admission the physical examination revealed an acutely and chronically ill-appearing, elderly, Caucasian male. He was confused, disoriented, aggressive and unable to express himself coherently. A Foley catheter was in place with evident bleeding around it. Temperature was 101.2° (rectal) and blood pressure 110/70. There were bilateral lenticular opacities and total edentia. The neck was supple with no venous distention. His chest revealed increased AP diameter, poor expansion bilaterally, and diminished breath sounds. The expiratory phase was prolonged with bibasilar rales. His heart was not enlarged and there was a regular sinus rhythm and an apical rate of 100. There were no audible murmurs; P2 was accentuated. The abdomen was soft with mild, diffuse tenderness but without evidence of guarding or rigidity. The liver edge was palpable 3 cm. below the right costal margin and was firm and non-tender. No other organs or masses were palpable. Rectal examination was negative. The remainder of the physical examination was not remarkable.

Admission laboratory studies revealed a hemoglobin of 16 gm., hematocrit 50%, leukocytes 31,000, with 98% neutrophils, 2% lymphocytes. Sedimentation rate was 1 mm. per hour. Urinalysis revealed red and white cells too numerous to count; 1+ albuminuria. Serum electrolytes were within normal range. Urine cultures grew *Pseudomonas aeruginosa*, sensitive to chloramphenicol; throat swab and sputum cultures grew alpha hemolytic Streptococcus. Blood urea nitrogen was 49 mg. per 100 ml. Chest roentgenogram revealed right ventricular preponderance, suggestive of cor pulmonale. There was no radiographic evidence of emphysema or pneumonitis. Electrocardiogram showed right ventricular hypertrophy and right atrial dilatation.

A working diagnosis of chronic renal disease (chronic pyelonephritis), acute cystitis or acute pyelonephritis, or both, was entertained. Therapy was initiated with chloramphenicol and tetracycline, and oral fluids were forced. He was placed on a moderately vigorous "antiasthmatic" regimen, consisting of saturated solution of potassium iodide, rectal aminophylline and meperidine. He was unable to cooperate to use intermittent positive pressure. On the third hospital day his blood pressure suddenly dropped to shock levels. He became clammy, cold, cyanotic and his pulse was rapid with poor volume. His confusion and agitation were replaced by lethargy which rapidly increased until he could not be aroused. He was given intravenous norepinephrine (4 μg. per 1000 ml. by rapid drip) but his blood pressure did not rise above 100 mm. Hg. Urinary output remained adequate. On decreasing the rate of flow of norepinephrine solution, the pressure would drop to shock levels. On the second day of continuous vasopressors, the patient's son arrived at the hospital and it was discovered that the patient had taken oral cortisone up until one month prior to admission. Dosage and duration of therapy were unknown, but it was suspected that the patient had taken the drug on an *ad lib* basis. He was immediately given an intravenous injection of hydrocortisone (200 mg.). The blood pressure rose to around 120/75 and within moments the patient's sensorium cleared for the first time since admission. Within 30 minutes vasopressors were discontinued. He was maintained on the antibiotics and gradually the oral hydrocortisone was decreased. By the fifth day he was on prednisone (5 mg. b.i.d.). His condition remained stable as the pyuria and albuminuria cleared.

Blood urea nitrogen decreased to normal and by the twenty-third hospital day the patient was discharged to continue on antibiotics and maintenance prednisone. Dosage of chloramphenicol and tetracycline was continued for 4 weeks and during this period the prednisone was gradually tapered and discontinued. He was advised as to the serious nature of his disability and given a "steroid wallet card."

COMMENT. This elderly man again demonstrated the phenomenon of steroid-induced adrenal unresponsiveness. He apparently had sufficient adrenal reserve to meet the minor stresses of everyday life, but when subjected to urethral dilatation, catheterization, cystitis and acute pyelonephritis, and a mild asthmatic attack, the added burden caused his adrenals to fail. One could argue for long-term adrenal insufficiency from illness and chronic stress, but the history of steroid ingestion, dramatic therapeutic response and ability to do well when steroids were discontinued, all suggest a steroid-induced adrenal unresponsiveness.

Discussion. Let us review the principal areas of steroid-induced adrenal insufficiency.

STEROID-INDUCED DISEASES. 1. *Hypercorticism and Cushingoid States.* There is little doubt that the most common and easily recognized of the complications attending the use of corticoids are hypercorticism or Cushingoid syndrome, or both. Symptoms may become manifest rapidly with sudden emergence of the full-blown clinical picture, or they may be delayed and insidious in onset. The classic elements of hypertension, moon facies, emotional lability, hyperglycemia and glycosuria, sodium retention and edema, potassium loss, nitrogen wasting with osteoporosis, may occur singly or in combinations (Adams and Siderius[1], Allanby[2], Moser[39], Nicholas, Wilson and Umberger[40], Polachek[44], Salassa *et al.*[46,47], Slaney and Brooke[51], Thorn *et al.*[57]). These symptoms may occur with varying severity depending to a certain degree on the magnitude of dose and duration of therapy.

A more occult, but quite significant spectrum of clinical syndromes was described by Slocumb and his associates[52,53]. These occurred among rheumatoid arthritis patients on long-term steroid therapy. Induced hypercorticism was observed to emerge as one of three distinct clinical configurations. They were: (1) evident periods of fatigability, weakness, arthralgia and emotional lability which were spaced between intervals of relative normalcy; (2) a "pan-angiitis-like state" characterized by fever, leukocytosis, elevated sedimentation rate, neuritis, thrombophlebitis and other "periarteritis nodosa like" symptoms; and (3) a syndrome similar to systemic lupus erythematosus with fever, anemia, renal and cutaneous lesions, and positive LE phenomena.

2. *Ulcers and Perforation in Ulcerative Colitis, Regional Ileitis and Diverticula.* The problem of peptic ulcers associated with steroids has been a constant hazard in prolonged therapy (Bloomfield[4], Bunim, Ziff and McEwen[6], DeBray *et al.*[11], Gray, Ramsey and Thorn[18], Hilbish and Black[22], Hirschowitz *et al.*[23], Kerdasha[28], Kern, Clark and Lukens[29], Lorber[35], Lucherini and Gospodinoff[36], Moser[39], Platt and Steinberg[43], Slocumb *et al.*[52,53], Weed, Bondy and Spiro[60], Zetzel[62]). Bunim recorded 5 cases of peptic ulcer occurring among 71 patients with rheumatoid arthritis on steroid therapy. All of these ulcer patients were receiving relatively high doses (Bunim, Ziff and McEwen[6]). It would seem that the incidence of steroid-induced ulcerations is a function of dose and duration of therapy. There is extensive evidence to corroborate the clinical im-

pression that synthetic steroids appear to provoke a higher incidence of peptic ulceration than older steroids (Bunim, Ziff and McEwen[6], Hollander[24], Lucherini and Gospodinoff[36], Moser[39], Stolzer *et al.*[56]). Zetzel[62] states that these ulcers are unusually large, demonstrate little of the usual inflammation and fibrosis and are associated with perforation in about 45% of cases. He observed that the relative frequency of gastric to duodenal ulcer is greater in the steroid-induced group, approximately 1:1 ratio in contrast to the usual 1:5. Since the work of Reifenstein and Spiro[45], who demonstrated that ACTH and cortisone administered to rats caused an accelerated excretion of acid-pepsin, this mechanism has been invoked to explain the phenomenon in humans. Patients with treated Addison's disease who develop chronic peptic ulceration have demonstrated a rise in uropepsin which roughly parallels the ulcer evolution. Other experiments have indicated that decreased mucous secretion, rather than increased acid-pepsin production, may be the mechanism (Zetzel[62]). Weed, Bondy and Spiro[60] studied 5 patients with duodenal ulcers in comparison to 5 others with benign ulcers and found no abnormality of adrenal function in either group as measured by plasma cortisol and corticosterone assay.

There are other untoward effects upon the gastrointestinal tract which are less common. Among these are occult perforation in regional enteritis (Kirsner, Palmer and Klotz[31], Machella and Hollan[37], Sauer, Brown and Dearing[48]) and diverticula (Palmer, Mason and Adams[42]). Of particular interest are the reports regarding the use of steroids in ulcerative colitis (Brown and McAuley[5], Elliott and Giansiracusa[15], Elliott, Kiefer and Hurxthal[16], Fierst *et al.*[17], Gray *et al.*[19], Halsted *et al.*[20], Kirsner and Palmer[30], Kirsner, Sklar and Palmer[32,50], Sauer, Dearing and Wallaeger[49], Tulin, Kern and Almy[59], Wirts, Rehfuss and Yantes[61]). Initial enthusiasm has been tempered by a moderate but significant incidence of bowel perforation in some series. The use of steroids beyond 2 weeks without clinical improvement is hazardous. Complete disintegration of the colon with mucosal destruction and adherence of contiguous bowel to abdominal wall has been observed following prolonged therapy. Perforations with synthetic steroids are apparently rare, but bleeding may be more frequent than with the older steroids. Kirsner, Sklar and Palmer[32] recommend therapy of ulcerative colitis by conventional methods with steroids employed as adjunctive therapy.

3. *Pancreatic Lesions.* Steroids have been employed in acute hemorrhagic pancreatitis to combat vascular collapse. Therefore, it is of great interest to note the report of Carone and Liebow[7] in which postmortem evidence of acute pancreatitis or peripancreatic fat necrosis, or both, was noted in 28.5% of 54 patients treated with ACTH or various steroids for other diseases. Ectasia of pancreatic acini was seen in 59% of hormone-treated patients and in 24% of controls. It is postulated that steroids may interfere with pancreatic activity by altering secretions and obstructing acini with release of pancreatic enzymes.

4. *Hepatomegaly with Fatty Infiltration.* A case of hepatomegaly due to fatty infiltration was reported by Steinberg, Webb and Rafsky[55]. This occurred in a patient receiving steroid therapy for acute rheumatic fever. Hepatic biopsy was observed to return to normal upon cessation of therapy. Hyperlipemia related to possible steroid-induced acceleration of fat mobilization has been demonstrated in laboratory animals.

4. *Osteoporosis.* This unfortunate complication would normally be considered under the negative nitrogen balance of Cushingoid syndrome, but its prevalence justified a separate word. Compression fractures of the spine secondary to induced osteoporosis has a disturbing incidence among elderly patients being treated with steroids (Curtiss, Clark and Herndon[10], Demartini *et al.*[12]). The negative protein balance causes a depletion of bone matrix. According to Craddock[9] these fractures occur most commonly in the lumbosacral vertebrae and pelvis. More rarely they have developed in knees, ankles and subastragalar joints.

6. *Hematologic Aberrations.* Various contradictory hematologic complications have been attributed to steroids. Fortunately, these are quite rare. Cosgriff[8] reported 39 instances of thromboembolic episodes in 28 patients out of 700 receiving steroids. Eighty-two per cent of these vascular complications occurred among patients receiving full dosage and all demonstrated hypercoagulability. This may be related to the accelerated hyperlipemia noted previously. The hypercoagulability may persist for 3 weeks after cessation of therapy.

Others (Denko and Schroeder[13]) have reported purpura and ecchymoses associated with increased capillary fragility. No associated evidence of coagulation defects were reported. Rarely, hemolytic anemia and LE phenomenon have been observed.

7. *Steroid Withdrawal Syndrome.* Another curious syndrome occurs in patients in whom steroid therapy is withdrawn abruptly. These people develop headache, anorexia, nausea, vomiting, myalgia, malaise, arthralgia, polyuria, restlessness, fatigability and occasionally the symptoms of acute labyrinthitis. Prompt reversal can be obtained by reinstituting steroid therapy and effecting a more gradual withdrawal (Henneman *et al.*[21]). This was regarded as a mild adrenal crisis. Slocumb *et al.*[52,53] comment on the similarity of "hypocorticism" arthralgia and that seen with hypercorticism.

8. *Infection Potentiating Effects.* (Editorial[14], Jacobs and Rose[25], Kass and Finland[26], Mills *et al.*[38], Oatway and Paulsen[41]). There has been increasing awareness of the fact that steroids, in addition to masking many of the classic manifestations of infection, may actually potentiate the virulence of infection. The capacity of steroids to foment a fulminating dissemination of tuberculosis in patients not under antituberculous chemotherapy was a fact learned through tragic experience (Oatway and Paulsen[41]). There has been increasing cognizance of the ability of steroids to provoke severe staphylococcal septicemia or septic arthritis, or both, with minimal clinical manifestations and poor antibiotic response (Mills *et al.*[38]).

Stefanini and Allegra[54] cite the rising incidence of fungus infections occurring in leukemia and lymphoma patients since steroids have been added to the regimen. Torack[58] observed that fungi proliferate on tissue surfaces when antibiotics alone were employed; but that systemic invasion occurred when antibiotics were combined with steroids.

Yet in all fairness, one must recall that steroids have a definite place in the therapy of infectious disease when used in conjunction with appropriate antibiotics. Steroids have been lifesaving in the early stage of overwhelming infection from typhus and typhoid. These are diseases which may kill before antibiotic effect is manifest or antibody protection galvanized. Certainly in the therapy of meningococcemia and probably in many other acute infectious processes concomitant therapy has a rational position.

9. *Adrenal Exhaustion Syndrome.* Of

all the abject conditions in which steroid therapy has been indicted, the most esoteric and pernicious is steroid-induced adrenal insufficiency. Kepler *et al.*[27] observed that many patients with unilateral adrenal hyperplasia or adenoma, upon whom unilateral adrenalectomy was performed, revealed the contralateral adrenal gland to be small and hypoplastic. These patients would develop severe Addisonian crisis within 12 to 48 hours postoperatively and would die after a period of relentless decline unless treated. Exogenous adrenal cortical hormones administered prophylactically and in maintenance have largely obviated this problem. However, in the wake of widespread steroid therapy for diseases far removed from adrenal replacement, we have come to appreciate a syndrome of induced "Addison's Disease" (Adams and Siderius[1], Allanby[2], Moser[39], Nicholas, Wilson and Umberger[40], Salassa *et al.*[46,47], Slaney and Brooke[51]). Similar to the true process, this therapy-induced syndrome may represent grades of adrenal depression. It is generally conceded that exogenous corticosteriods can induce prolonged and probably permanent suppression of adrenal function. The duration of this period of "adrenal unresponsiveness" is variable. The limits of time from cessation of therapy to onset of stress situation, of dosage and duration of therapy are not clearly defined. However, as little as 100 mg. of cortisone given over a 5-day period has been suspected of provoking significant adrenocortical suppression (Salassa *et al.*[46]).

Lewis *et al.*[34] reported the first case of steroid-induced adrenal exhaustion syndrome precipitated by a surgical procedure. The comprehensive surveys by Salassa *et al.*[46,47] and others (Bennett[3]) focused attention on this vulnerable group of patients who had received steroid therapy upon some prior occasion for an unrelated disease, and who developed profound unrelenting vascular collapse following performance of surgery. This disturbance was unresponsive to vasopressor and colloid replacement medication. Subsequently, this phenomenon has been observed to follow a wide range of "stress situations." These have included major and minor surgery (Adams and Siderius[1], Nicholas, Wilson and Umberger[40], Salassa *et al.*[46,47], Slaney and Brooke[51]), orthopedics (Nicholas, Wilson and Umberger[40]) (closed and open reductions), normal parturition, burns, accidents, and others. While there has been a logical speculation that this condition could develop as a result of serious medical illness, there is little recorded experience in this area (Moser[39]). Slocumb *et al.*[52,53] and Larylere *et al.*[33] feel that patients are relatively free of this hazard when 6 months to 2 years have elapsed since cessation of steroid therapy. However, it must be noted that in Case 1, the patient had not received steroid therapy for 3 years. It is readily conceded that one can never exclude the possibility of a spontaneous Addison's disease having supervened in these cases, or that a long-standing subclinical Addison's state was aggravated to clinical threshold by steroid therapy. It is a well recognized clinical fact that a prolonged debilitating illness is capable of inducing adrenal depletion. It would not be remiss to speculate that perhaps the patient under the stress of chronic medical illness, who is perilously near to exhausting his adrenal reserve, may be "pushed toward the line" of adrenal decompensation by exogenous steroids, which act upon the anterior pituitary to cease critical ACTH production. This patient may function at a low level of adrenal function, adequate to meet the minor stresses of normal living, and yet not

deficient to the point of permitting the stigmata or symptoms of adrenal insufficiency to emerge. However, if we add to this tenuous situation, stress of a sufficient magnitude, it may "push him over the line" into frank adrenal insufficiency. The "stressful situation" may be medical as well as surgical. The frank suspicion remains that any deaths attributed to "therapeutic refractoriness" may have been related to unappreciated therapy-induced adrenal insufficiency.

The alert physician will make careful inquiry into the steroid history of every patient for whom any arduous diagnostic or surgical procedure is contemplated. If the patient is unable to give a cogent history, the family should be interrogated intensively regarding steroid ingestion, arthritis, asthma, dermatological lesions or any other situation in which steroid therapy might have been given. One must also be alert for the patient with a clear-cut medical illness in whom vigorous, properly conceived and executed therapy has been ineffective. If he continues to decline despite all efforts adrenal unresponsiveness must be suspected and treated.

In this situation it is mandatory that the patient receive hydrocortisone prophylactically. We have employed hydrocortisone (up to 300 mg. daily intravenously) or its synthetic equivalent by mouth, for the first 3 days. After this, dosage, mode of administration of therapy, and duration is dictated by clinical response. Slow tapering is always essential to prevent exacerbation of the process being treated, or the withdrawal effects of the drug, *per se*. Often it may be necessary to provide maintenance therapy for a prolonged period; or perhaps for the duration of the patient's life if severe adrenal impairment has been demonstrated. Every patient should be instructed regarding the vagaries of the drug he has taken, advised about future "stressful situations" and informed that he must include this information in any future history given to a physician. He should be given a "steroid wallet card" which will contain the name of the particular drug, dosage, duration of therapy, disease for which it has been administered, and name of the prescribing physician. In the event of disaster or the occurrence of some serious medical disease in which the patient is unable to give a history, the card will provide the perplexed attending physician with an appreciation of the peculiar category of his patient.

From the foregoing tales of steroid woes, it would seem apparent that every physician should exercise the greatest caution and discrimination in selecting patients for steroid therapy. If proper indication exists, steroids should be delivered with thankfulness for their incredible therapeutic benefit; but with equal respect for their toxicity. Carelessness, "shot gun" therapy to "see what steroids will do," or ignorance regarding the potential dangers implicit in this medication are all a prelude to disaster.

Summary and Conclusions. 1. We have presented 4 patients demonstrating widely divergent medical diseases, yet each of whom revealed the following pertinent features in common.

a) Response to vigorous, well-conceived and properly executed medical therapy was poor, and all patients lapsed into a state of relentless decline.

b) It was suspected that the patients were suffering from adrenal unresponsiveness and steroid therapy was initiated in addition to the conventional therapy for the underlying process.

c) The institution of steroid therapy was attended by a prompt improvement and loss of refractoriness to prior therapy.

d) Each patient had been on steroid therapy for an unrelated illness at some time in the past, and for one reason or another was unable to present this information to the ward officer on admission.

2. A plea is made for the physician to include "steroid-induced adrenal insufficiency" in his differential diagnosis of the patient who has a severe medical illness and who is unresponsive to conventional therapy.

3. We add our voices to the swelling chorus that beseeches prudence and caution in the administration of steroid hormones.

REFERENCES

1. **Adams, R.**, and **Siderius, N.**: J. Am. Med. Assn., **165,** 41, 1957.
2. **Allanby, K. D.**: Lancet, **1,** 1104, 1957.
3. **Bennett, W. A.**: Proc. Staff. Meet., Mayo Clin., **28,** 658, 1953.
4. **Bloomfield, A. L.**: A.M.A. Arch. Int. Med., **90,** 281, 1952.
5. **Brown, G. M.**, and **McAuley, J. S.**: J. Am. Med. Assn., **150,** 1587, 1952.
6. **Bunim, J. J., Ziff, M.**, and **McEwen, C.**: Bull. Rheumatic Dis., **5,** 73, 1954.
7. **Carone, F. A.**, and **Liebow, A. A.**: New England J. Med., **257,** 690, 1957.
8. **Cosgriff, S. W.**: J. Am. Med. Assn., **147,** 924, 1951.
9. **Craddock, W. L.**: U.S. Armed Forces Med. J., **8,** 907, 1957.
10. **Curtiss, P. H., Jr., Clark, W. S.**, and **Herndon, C. H.**: J. Am. Med. Assn., **156,** 467, 1954.
11. **DeBray, C., Hardouis, J. P., Laumonier, R., Cerf, M.**, and **Martin, E.**: Semaine Hôp. Paris, **32,** 3616, 1956.
12. **Demartini, F., Boots, R. H., Snyder, A. I., Sandson, J.**, and **Ragan, C.**: J. Am. Med. Assn., **158,** 1505, 1955.
13. **Denko, C. W.**, and **Schroeder, L. R.**: Ibid., **164,** 41, 1957.
14. Editorial: New England J. Med., **258,** 663, 1958.
15. **Elliott, J. M.**, and **Giansiracusa, J. E.**: Ibid., **250,** 969, 1954.
16. **Elliott, J. M., Kiefer, E. D.**, and **Hurxthal, J. M.**: Ibid., **245,** 288, 1951.
17. **Fierst, S. M., Robinson, E., Langsam, A., Werner, A.**, and **Ingegno, A. P.**: J. Am. Med. Assn., **163,** 1444, 1957.
18. **Gray, S. J., Ramsey, C. G.**, and **Thorn, G. W.**: Ann. Int. Med., **45,** 73, 1956.
19. **Gray, S. J., Reifenstein, R. W., Benson, I. A., Jr.**, and **Young, J. C. G.**: J. Am. Med. Assn., **148,** 1489, 1952.
20. **Halsted, J. A., Adams, W. S., Sloan, S., Walters, R. L.**, and **Bassett, S. H.**: Gastroenterology, **19,** 698, 1951.
21. **Henneman, P. H., Wang, D. M. K., Irwin, J. W.**, and **Burrage, W. S.**: J. Am. Med. Assn., **158,** 384, 1955.
22. **Hilbish, T. F.**, and **Black, R. L.**: A.M.A. Arch. Int. Med., **101,** 932, 1958.
23. **Hirschowitz, B. I., Streeten, D. H. P., Pollard, H. M.**, and **Boldt, H. A., Jr.**,; J. Am. Med. Assn., **158,** 27, 1955.
24. **Hollander, J. L.**: Lecture to medical house staff at Brooke Army Hospital, BAMC, Fort Sam Houston, Texas, on 24 February 1959.
25. **Jacobs, J. H.**, and **Rose, F. C.**: Tubercle, **36,** 113, 1955.
26. **Kass, E. H.**, and **Finland, M.**: Ann. Rev. Microbiol., **7,** 361, 1953.
27. **Kepler, E. J., Kennedy, R. L. S., Davis, A. A., Walters, W.**, and **Wilder, R. M.**: Proc. Staff Meet., Mayo Clin., **9,** 169, 1934.
28. **Kerdasha, R.**: J. Med. Soc. New Jersey, **50,** 343, 1953.
29. **Kern, F., Clark, G. M.**, and **Lukens, J. G.**: Gastroenterology, **33,** 25, 1957.
30. **Kirsner, J. B.**, and **Palmer, W. L.**: Ann. Int. Med., **41,** 232, 1954.
31. **Kirsner, J. B., Palmer, W. L.**, and **Klotz, A. P.**: Gastroenterology, **20,** 229, 1952.
32. **Kirsner, J. B., Sklar, M.**, and **Palmer, W. L.**: Am. J. Med., **22,** 264, 1957.
33. **Larylere, R. G., Barthold, E. A., Willett, F. M., Feichtmeir, T. U., Wilson, L.**, and **Engleman, E. P.**: A.M.A. Arch. Int. Med., **99,** 888, 1957.
34. **Lewis, L., Robinson, R. F., Yee, J., Hacker, L. A.**, and **Eisen, G.**: Ann. Int. Med., **39,** 116, 1953.
35. **Lorber, J.**: Brit. Med. J., **2,** 749, 1957.
36. **Lucherini, T.**, and **Gospodinoff, A.**: Minerva med., **47,** 867, 1956.
37. **Machella, T. E.**, and **Hollan, O. R.**: Am. J. Med. Sci., **221,** 501, 1951.

38. **Mills, L. C., Boylston, B. F., Greene, J. A.,** and **Moyer, J. H.:** J. Am. Med. Assn., **164,** 1310, 1957.
39. **Moser, R. H.:** Diseases of Medical Progress. Springfield, Ill.: Charles C Thomas, in press.
40. **Nicholas, J. A., Wilson, P. D.,** and **Umberger, C. J.:** J. Am. Med. Assn., **164,** 261, 1957.
41. **Oatway, W. H., Jr.,** and **Paulsen, G. A.:** Arizona Med., **12,** 275, 1955.
42. **Palmer, T. H., Mason, P. J. H.,** and **Adams, A. C.:** J. Maine Med. Assn., **46,** 349, 1955.
43. **Platt, W. D.,** and **Steinberg, I. H.:** New England J. Med., **256,** 823, 1957.
44. **Polachek, A. A.:** Maryland Med. J., **4,** 195, 1955.
45. **Reifenstein, G. S.,** and **Spiro, H. M.:** J. Lab. & Clin. Med., **35,** 899, 1958.
46. **Salassa, R. M., Bennett, W. A., Keating, F. R., Jr.,** and **Sprague, R. G.:** J. Am. Med. Assn., **152,** 1509, 1953.
47. **Salassa, R. M., Keating, F. R., Jr.,** and **Sprague, R. G.:** Proc. Staff Meet., Mayo Clin., **28,** 662, 1953.
48. **Sauer, W. G., Brown, P. W.,** and **Dearing, W. H.:** Gastroenterology, **22,** 550, 1953.
49. **Sauer, W. G., Dearing, W. H.,** and **Wallaeger, E. E.:** Proc. Staff Meet., Mayo Clin., **28,** 641, 1953.
50. **Sklar, M., Kirsner, J. B.,** and **Palmer, W. L.:** Ann. Int. Med., **46,** 1, 1957.
51. **Slaney, G.,** and **Brooke, B. N.:** Lancet, **1,** 1167, 1957.
52. **Slocumb, C. H.:** Bull. Rheumat. Dis., **3,** 39, 1952.
53. **Slocumb, C. H., Polley, H. F., Ward, L. E.,** and **Hench, P. C.:** Ann. Int. Med., **46,** 86, 1957.
54. **Stefanini, M.,** and **Allegra, S.:** New England J. Med., **256,** 1026, 1957.
55. **Steinberg, H., Webb, W. M.,** and **Rafsky, H. A.:** Gastroenterology, **21,** 304, 1952.
56. **Stolzer, B. L., Barr, J. H., Eisenbris, C. H., Jr., Wechsler, R. L.,** and **Margolis, H. M.:** J. Am. Med. Assn., **165,** 13, 1957.
57. **Thorn, G., Jenkins, D., Laidlaw, J. C., Goetz, F. C., Dingman, J. F., Arons, W. L., Streeten, D. H. P.,** and **McCracken, B. H.:** New England J. Med., **248,** 232, 284, 323, 369, 414, 588, 632, 1953.
58. **Torack, R. M.:** Am. J. Med., **22,** 872, 1957.
59. **Tulin, M., Kern, F., Jr.,** and **Almy, T. P.:** J. Am. Med. Assn., **150,** 562, 1952.
60. **Weed, R. I., Bondy, P. K.,** and **Spiro, H. M.:** New England J. Med., **258,** 700, 1958.
61. **Wirts, C. W., Rehfuss, M. E.,** and **Yantes, H. A.:** J. Am. Med. Assn., **154,** 36, 1954.
62. **Zetzel, L.:** New England J. Med., **257,** 1170, 1957.

SUMMARIO IN INTERLINGUA

Effecto Aggravatori de un Sever Morbo Medical Super un Insufficientia Adrenal Inducite per Therapia Steroide

Es presentate le casos de 4 patientes con divergentissime morbos medical qui nonobstante exhibiva in commun le sequente characteristicas pertinente:

a) Le responsa a un vigorose, ben planate, e ben executate therapia medical esseva mal, e omne le 4 patientes entrava in un stato de declino progressive.

b) Esseva suspicite que le patientes suffreva de non-responsivitate adrenal, e un therapia steroide esseva instituite in supplementation del therapia conventional pro le processo subjacente.

c) Le institution del therapia steroide esseva sequite per un prompte melioration clinic e per le perdita del refractorietate al therapia specific.

d) Omne le 4 patientes habeva recipite therapia steroide pro un altere morbo al un o al altere tempore in le passato e pro diverse rationes non poteva communicar iste information al agentes registratori al tempore de lor hospitalisation.

Es recommendate urgentemente que le medico include "insufficientia adrenal a induction steroide" in le diagnose differential de casos in que le patiente ha un sever morbo medical que non responde al therapia conventional.

Le autores junge lor voces al crescente choro de autoritates qui demanda plus alte grados de prudentia e de circumspection in le uso de hormones steroide.

A PRELIMINARY STUDY ON THE CLINICAL USE OF CHOLINE SALICYLATE*

By Captain George M. Davis, MC, USN
OAKLAND, CALIFORNIA

Captain Paul T. Moore, MC, USN

Lt. CDR. Jan K. Siemsen, MC, USNR

Lt. Jonas Sode, MC, USNR

AND

Lt. William J. Baker, MC, USN
GREAT LAKES, ILLINOIS

(From the Medical Services, U.S. Naval Hospitals, Oakland, California [Dr. Davis], and Great Lakes, Illinois [Drs. Moore, Siemsen, Sode and Baker])

Although so many new and effective drugs have been developed during recent years, salicylates, and aspirin in particular, retain their unchallenged position as the most widely used of all drugs and are regarded by many as the drug of choice in the treatment of rheumatic fever and various arthritides. Yet, in spite of their undeniable advantages, most available salicylates possess certain undesirable traits.

The administration of sodium salicylate in large doses is considered undesirable in many patients with cardiovascular, renal and hepatic disorders. Aspirin, as is well known, is prone to induce gastrointestinal distress and even gastric hemorrhage (Cossar[3], Lange[8]) in a significant number of patients and such side effects may preclude its use in therapeutic dosages required for optimal results. Moreover, it is not only relatively insoluble but is unstable in aqueous suspension. Thus aspirin is not easily adaptable for administration as a liquid which may be the most acceptable form for administering drugs to children and the more cachetic older patients who experience difficulty in swallowing tablets, particularly in large numbers.

Quite recently, a new salicylate, choline salicylate, has been described as possessing properties of apparent interest (Broh-Kahn[2]). Extremely water-soluble in the form of a stable aqueous solution, it may readily be administered to patients of all ages. It is apparently absorbed, when given by mouth, five times as rapidly as aspirin (Broh-Kahn[2], Wolf and Aboody[10]) and the collected experience to date is said to indicate that it may induce a lesser frequency of gastrointestinal distress (Broh-Kahn[2]). In view of these described properties and the well established role of salicylate therapy in various diseases, it appeared appropriate to study its effects in patients for whom salicylates are indicated. The following presents our own preliminary observations of the use of choline

*The opinions or assertions contained herein are those of the authors and are not to be construed as official or necessarily as reflecting the views of the Medical Department of the Navy or the Naval Service at large.

salicylate in rheumatic fever in particular, as well as in certain types of arthritis.

Material and Methods. During the earlier phases of our study, choline salicylate* was used in the form of a clear, cherry-flavored aqueous solution, each teaspoonful (5 ml.) of which contained 509 mg. of choline salicylate. Later, the drug was administered in a concentration of 870 mg. of choline salicylate per 5 ml. of the solution. In this latter form, each teaspoonful provides the equivalent of 10 gr. of aspirin in terms of salicylate content.

Although we have given the drug to well over 100 patients with a variety of conditions and complaints, this report is confined to a consideration of the results of its administration to 35 patients whose clinical course it was possible to observe and record with a satisfactory degree of control and accuracy. These included 25 patients with acute rheumatic fever and 8 with rheumatoid arthritis, who received choline salicylate daily for periods up to 7 weeks. In the group with rheumatic fever, an attempt was made to analyze the response to treatment and the tolerance and acceptance in comparison to acetylsalicylic acid; in the others, only tolerance and acceptance were evaluated because of the small number of patients and the notoriously variable course of these conditions.

Results. RHEUMATIC FEVER. All patients in this group were considered to have proven rheumatic fever in accordance with a modified Jones' criterion (Friedberg[5]). Twenty-one had acute polyarthritis when treatment was started; 14 had evidence of carditis manifested by electrocardiographic abnormalities and significant murmurs. None was in congestive failure; all patients were Caucasian males, 17 to 32 years of age, with a mean age of 20.5 years.

Twenty-two patients were started on choline salicylate as the only medication on the first to fifth hospital day as soon as the diagnosis was established, whereas the other 3 had been given acetylsalicylic acid prior to receiving choline salicylate. The daily dose of choline salicylate ranged from 4.8 to 15.75 gm. Most patients were started on a dosage of 10 to 15.75 gm. which was reduced after 4 to 14 days; the maintenance dose was 11.5 gm. in 12, 10 gm. in 7, and 7 gm. in 6 patients. The medication was given in divided doses every 4 or 6 hours.

The duration of therapy ranged from 20 to 49 days with a mean of 34.5 days. The clinical and laboratory responses were considered satisfactory in 24 of the 25 patients. One failed to show any defervescence or improvement of the polyarthritis after 7 days' treatment with 14.4 gm. of choline salicylate, but subsequently responded dramatically to steroid therapy, becoming afebrile and asymptomatic in 48 hours.

Acute polyarthritis, present in 21 patients at the initiation of choline salicylate therapy, subsided completely within 3 to 9 days in 20 patients. Significant temperature elevation (above 100° F.) present in 20 patients disappeared in 19 within 1 to 4 days. The corrected sedimentation rate was elevated at the onset of treatment in 22 patients and returned to normal values in 21 within 6 to 34 days, with an average of 21.5 days. C-reactive protein was present in the serum of 21 patients at the beginning of therapy and disappeared in 20 within 8 to 30 days, averaging 13.5 days. Electrocardiographic abnormalities, namely, first degree heart block and nonspecific repolarization changes, were found in 12 patients at the beginning of choline salicylate therapy and disappeared in all of these within 3 to 9 days. Cardiac murmurs were not evaluated in relation to treatment.

OTHER ARTHRITIC CONDITIONS. While any definitive analysis of the response to choline salicylate treatment is impossible in this small group of 8 pa-

*Kindly supplied in the form of Arthropan by The Purdue Frederick Company, New York City.

tients with rheumatoid arthritis, one with gout, and another with serum sickness, it was our general impression that the responses were altogether comparable to those obtained with equivalent doses of acetylsalicylic acid. Superficially at least, such a conclusion appears permissible, since 8 of the 10 patients had been on acetylsalicylic acid prior to choline salicylate treatment and the opportunity was thus afforded to compare their responses to the two drugs. In this group, the dosage of acetylsalicylic acid employed was increased to the limits of tolerance as indicated by the development of tinnitus or pyrosis, or both. The maximal tolerated dosage thus determined ranged from 75 to 180 grains daily. In the case of choline salicylate, the daily dosages used were from 11.5 to 20.9 gm. In terms of salicylate content, these latter dosages are equivalent to 140 and 240 grains of aspirin, respectively. As noted above, the therapeutic responses of the patients to equivalent dosages of the two drugs impressed us as comparable. A more detailed comparison of the tolerance to the two drugs follows:

SIDE EFFECTS.- As could be expected, some side effects typical of salicylism were observed with the large doses of choline salicylate used in this study. Of the symptomatic ones, tinnitus and pyrosis were the only ones encountered. In the series of 25 patients with acute rheumatic fever, these symptoms developed in 4 patients on 11.5 gm. daily and in 4 on 7.0 gm. daily. The symptoms in these 8 cases were mild, readily controlled and necessitated neither interruption nor reduction of dosage. In 3 other patients receiving a similar range of dosages, these symptoms were severe enough to render reduction of the dosage advisable and they tolerated the reduced amounts of choline salicylate well.

Laboratory tests also indicated transient abnormalities. As is the case with aspirin (Cossar[3], Lange[8]), intermittently positive guaiac tests (from a trace to 2+), were noted in 6 of the 25 patients with acute rheumatic fever, in one of whom a rectal polyp could be indicated as the responsible factor. After choline salicylate was discontinued, the occult blood disappeared from the stool of the other 5.

Reducing substances were found intermittently in the urines of 12 of the 25 patients with rheumatic fever, as shown by positive "clinitests" (1+ to 3+). This phenomenon disappeared in all cases after choline salicylate was discontinued, but fasting and postprandial blood sugars were within normal limits in all patients showing this reaction. On 10 occasions specimens of the same urine showing a positive reaction to "clinitest" were checked with "Testape" and found to be negative for glucose. This would confirm the well known fact that a reducing substance appears in the urine of patients receiving salicylate but it is not a sugar (Goodman and Gilman[6]). It is likely that the higher the content of this reducing substance, the higher the blood level of salicylate. Moreover, it has been repeatedly demonstrated that salicylates may exert a hypoglycemic effect and an actual reduction of a pre-existing diabetic glycosuria (Reid, MacDougall and Andrews[9]).

In contrast to the above findings, "clinitests" were consistently negative or showed only rarely a trace to 1+ in a comparable group of patients who received equivalent doses of acetylsalicylic acid.

Patient acceptance of choline salicylate was almost uniformly satisfactory. In the group of 25 with rheumatic fever, 7 patients stated, on questioning, that after prolonged treatment they developed a distaste for the prepara-

tion. Subsequent experience of our own, as well as of others (Guild[7]), indicates that many of these objections can be dissipated either by diluting the dose in water or swallowing some water after the medication, or both. Fourteen others of this group expressed no objections whatever to the medication and 4 declared it to be distinctly pleasant to take.

Comparative Tolerance to Choline Salicylate and Aspirin. An opportunity arose during this study to observe the reactions, both to aspirin and choline salicylate, of 11 patients who had received each drug over a period of time. Three of these, from the group with rheumatic fever, had experienced moderate to marked tinnitus and pyrosis on daily doses of 90 to 120 grains of aspirin. These side effects disappeared completely when their treatment was changed to equivalent quantities of choline salicylate and all 3 patients accordingly expressed a marked preference for it.

Eight individuals in the group with rheumatoid and other types of arthritis likewise had been exposed to both drugs. In these, tinnitus and pyrosis developed on daily doses of aspirin ranging from 75 to 180 grains. Acetylsalicylic acid was then discontinued and choline salicylate was given in equivalent dosage. In 2 of these patients, the tinnitus and pyrosis immediately subsided. Thus, one with a previously diagnosed active duodenal ulcer, who complained of increased gastric distress on 120 grains of aspirin, subsequently tolerated well the equivalent quantity, 11.5 gm., of choline salicylate.

In the other 6 cases, the side effects encountered on aspirin continued to develop when choline salicylate was administered in equivalent dosage but subsided when the dose was decreased to a level corresponding to that of acetylsalicylic acid which had been well tolerated previously.

Thus, of the 11 patients who received both aspirin and choline salicylate, 5 exhibited a greater degree of tolerance to the latter. In none of the 11 was the tolerance to acetylsalicylic acid superior to that of choline salicylate. In general, these observations confirm those of others who have reported that a significant number of patients tolerated larger dosages of choline salicylate than of aspirin, particularly those with a history of gastric distress associated with the latter. It has been pointed out that the gastric distress elicited by acetylsalicylic acid precludes its use in the dosages (up to tinnitus) required for optimum treatment of this type of patient with rheumatoid arthritis in particular, and that choline salicylate may be used to advantage in such patients (Feldman[4]).

Summary and Conclusions. Since a critical analysis of the clinical effectiveness of choline salicylate would require more extensive and controlled study on a large group of patients, our impressions based on this preliminary study can be stated as follows:

The antipyretic and anti-inflammatory effects of choline salicylate in rheumatic fever appear to be comparable to those of acetylsalicylic acid in corresponding doses, if the present series is compared with previous experiences at this hospital (Bates[1]).

The anti-inflammatory and analgesic effects of choline salicylate in rheumatoid arthritis appear to be comparable to those of equivalent doses of acetylsalicylic acid.

As a rule, in conventional therapeutic dosages for these conditions, tolerance and acceptance of choline salicylate are good, and side effects, insignificant.

In our series, a significant number of patients receiving both choline salicy-

ate and aspirin tolerated larger dosages of choline salicylate. None tolerated large dosages of acetylsalicylic acid.

It is suggested that choline salicylate may be particularly valuable in patients who experience marked side effects on comparable dosages of acetylsalicylic acid.

Choline salicylate appears to be a valuable addition to the therapeutic armamentarium and deserves further and more extensive evaluation.

ACKNOWLEDGMENT: The authors wish to express their appreciation for the counsel and suggestions of Alvin F. Coburn, M.D., of New York City.

REFERENCES

1. **Bates, R. C.:** Ann. Int. Med., **48**, 1017, 1958.
2. **Broh-Kahn, R. H.:** Fed. Proc., **18**, 17, 1959.
3. **Cossar, I. A.:** Lancet, **1**, 539, 1959.
4. **Feldman, H. A.:** Personal communication.
5. **Friedberg, C. K.:** Diseases of the Heart. Philadelphia: W. B. Saunders Co., pp. 743-747, 1949.
6. **Goodman, L. S.**, and **Gilman, A.:** The Pharmacological Basis of Therapeutics, 2nd ed. New York: The Macmillan Co., p. 286, 1956.
7. **Guild, H. G.:** Personal communication.
8. **Lange, H. F.:** Gastroenterology, **33**, 770, 1957.
9. **Reid, J., MacDougall, A. I.**, and **Andrews, M. M.:** Brit. Med. J., **2**, 1071, 1957.
10. **Wolf, J.**, and **Aboody, R.:** Fed. Proc., **18**, 605, 1959.

SUMMARIO IN INTERLINGUA

Studio Preliminari del Uso Clinic de Salicylato de Cholina

Un analyse critic del efficacia clinic de salicylato de cholina requirerea un plus extense controlate studio in un grande numero de patientes. Le presente studio, ben que de character preliminari, permitte nonobstante le formulation del sequente impressiones:

Le effectos antipyretic e anti-inflammatori de salicylato de cholina in febre rheumatic es apparentemente comparabile a illos de acido acetylsalicylic in doses correspondente. Iste observation es basate super le comparation del presente serie con previe experientias in le mesme hospitales reportate per Bates in 1958.

Le effectos anti-inflammatori e analgesic de salicylato de cholina in arthritis rheumatoide es apparentemente comparabile a illos de equivalente doses de acido acetylsalicylic.

A generalmente parlar, le tolerantia pro salicylato de cholina e le acceptation de illo in le doses que es conventionalmente usate in le tractamento del conditiones mentionate es bon. Le effectos lateral es non-significative.

In nostre serie, un numero de patientes recipiente tanto salicylato de cholina como etiam aspirina tolerava salicylato de cholina in plus grande doses. Nulle del patientes in le presente serie tolerava grande doses de acido acetylsalicylic.

Es suggerite que salicylato de cholina es forsan particularmente utile in patientes qui manifesta marcate effectos lateral post doses comparabile de acido acetylsalicylic.

Salicylato de cholina pare esser un importante addition al armamentario therapeutic e merita evalutationes additional de plus extense dimensiones.

CURRENT PROBLEMS IN SALMONELLOSIS*

By Harrison F. Flippin, M.D.
ACTIVE HONORARY CONSULTANT, DEPARTMENT OF MEDICINE,
PHILADELPHIA GENERAL HOSPITAL (BLOCKLEY DIVISION),
PROFESSOR OF CLINICAL MICROBIOLOGY, THE GRADUATE SCHOOL OF MEDICINE,
THE UNIVERSITY OF PENNSYLVANIA

AND

George M. Eisenberg, Sc.D.†
CHIEF, DIVISON OF MICROBIOLOGY,
PHILADELPHIA GENERAL HOSPITAL (BLOCKLEY DIVISION),
ASSISTANT PROFESSOR IN CLINICAL MICROBIOLOGY, THE GRADUATE SCHOOL OF MEDICINE,
THE UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

(From the Department of Medicine and the Division of Microbiology, Department of Laboratories, Philadelphia General Hospital (Blockley Division), and the Section of Infectious Diseases, Department of Medicine, The University of Pennsylvania, Philadelphia, Pennsylvania)

Within the past 20 years important refinements in laboratory methods have contributed significantly to our knowledge concerning the true nature of infections involving the gastrointestinal tract. Of particular importance are the gastroenteritides caused by various Gram-negative organisms, including members of the genus Salmonella. Although a great deal has been learned concerning the bacteriology, serology, and epidemiology of salmonellosis, neither prophylaxis in, nor therapy for, this group of infections has attained a satisfactory state. The purpose of this presentation is to consider certain factors contributing to the salmonella problem.

SALMONELLOSIS. The term salmonellosis implies the infection of a human or animal by one or several of the more than 200 bacterial serotypes comprising the genus Salmonella. Included in this group are the organisms more familiarly known as the "typhoid-paratyphoid" bacilli. Thus, persons infected with either S. *typhosa* or S. *choleraesuis* are classified in each instance as having salmonellosis. A major difficulty in accepting this broad point of view stems from the older concept that infection with S. *typhosa* results in a serious septic disease, while infection with S. *paratyphi* A, B, or C is associated with less severe disease. However, greater familiarity with salmonellosis has resulted in the realization that any one of several clinical syndromes may be produced by the same or different salmonella serotypes.

EPIDEMIOLOGY. Salmonellae are found in all parts of the world and occur frequently among various species of lower animals (Edwards[2]). Not only do many different serotypes occur both in animals and man, but there is a distinct correlation between the presence of the organisms in the lower animals and in the human population in a given locality. However, the methods whereby the organisms are transmitted from animals to man and *vice*

*Presented in part before the Seventy-second Meeting of the American Clinical and Climatological Association, Hot Springs, Virginia, November 3, 1959.

†Deceased, October 26, 1959.

versa may vary from one region to another, depending upon sanitary facilities and habits of the populations. Both the human and veterinary medical literature abound with reports dealing with the presence of salmonellae in animals used widely as food and in animals which in one way or another come into close contact with man. Domestic fowl (turkeys, ducks, chickens) probably constitute the largest single reservoir of salmonellae among animals. The bacteria may gain entrance into eggs either as a result of ovarian infection or by penetration of the eggshell, thereby accounting for the high incidence of salmonellae in dried and frozen egg products. For many years, swine have been known to carry salmonellae and mass outbreaks of salmonellosis in man due to infected pork have often been reported. More recently, it has been noted that swine in abattoirs are much more frequently infected than animals on the farm, a fact which suggests the importance of the sales yard, the holding lot, and the abattoir in the spread of the organism. In many parts of the world salmonellosis is endemic in cattle and often has been transmitted to man through infected carcasses and milk. Other animals, such as dogs, cats and rats, snakes, tortoises and insects have been found to carry salmonellae. Salmonellae have been isolated also from fish and shellfish, gulls, ducks, and other animals that inhabit waters which have been contaminated with excreta of man or other terrestrial animals.

It is evident that salmonellosis is widely distributed throughout the animal kingdom and that salmonellae are to be encountered in many animal products. However, the role of the human carrier and the processing plant in the contamination of food products must not be underestimated. The literature contains many reports of outbreaks of salmonellosis caused by human carriers working in food processing plants. In fact, it has become apparent that the carrier state in food handlers occurs much more frequently than in the general population to the extent that it represents an occupational hazard of those persons who continuously handle contaminated food processing equipment or uncooked meats and animal carcasses. It is also well known that direct transmission from man to man may occur without the intervention of food, as exemplified by infants in hospital nurseries contracting infection from other infants or from asymptomatic staff members.

Recent reports (Edwards[2], MacCready, Reardon and Saphra[8], Saphra and Winter[11]) indicate that the number of infections with salmonellae other than S. *typhosa* has been increasing steadily and markedly in both man and lower animals during the past few years (Table 1). In 1955, we (Eisenberg, Palazzollo and Flippin[3]) emphasized that human infections with salmonellae other than S. *typhosa* may not be recognized because of the complexity of bacteriologic methodology involved in their isolation and identification and the protean character of the clinical manifestations. Hence, some of the reported rise in incidence may be the result of refinements in laboratory methods, an increased awareness of the disease on the part of the physician and a more complete reporting of cases. While some of the rise in incidence of salmonellosis probably has resulted from more complete reporting in the later years, the magnitude of the increase, especially in states that have long enjoyed good reporting, suggests that it may well be real.

Although it is difficult to make a categorical statement regarding the reasons for increased incidence of salmonellosis, several hypotheses present themselves:

1) It is known that improper hand-

ling of food and lack of adequate refrigeration are contributing factors in most outbreaks of salmonellosis. Thus, with our rapidly changing food habits, more and more food processing has escaped from the family kitchen into the hands of the large commercial manufacturers. Because of the difficulty of effective cleaning and sterilization of the complex machinery used for assembly line food processing, the mass preparation and transportation of packaged foods increases the risk of widespread contamination with salmonellae. Likewise, the dispensing of foods in a greater number of public eating places may result in the poisoning of a large number of customers. It is not unreasonable to suppose that an increase in total number of eating places may be accompanied by an increase in total number of establishments with faulty sanitary facilities and employing more people with undesirable personal hygiene habits. The increase in the number of human carriers of salmonellae has supplied more opportunities for food to be infected by those handling it.

2) Protection against salmonellosis by vaccination is only relative and under conditions of heavy exposure infections may occur despite immunization. However, the marked decrease in infections caused by *S. typhosa* is related in part to the widespread use of typhoid vaccine. Since the vaccine commonly used in this country contains only *S. typhosa*, *S. paratyphi*, and *S. schottmuelleri* (typhoid-paratyphoid A and B bacilli) and affords no protective immunization against Group C salmonellae, this may explain in part the comparatively high incidence of infections caused by members of this group.

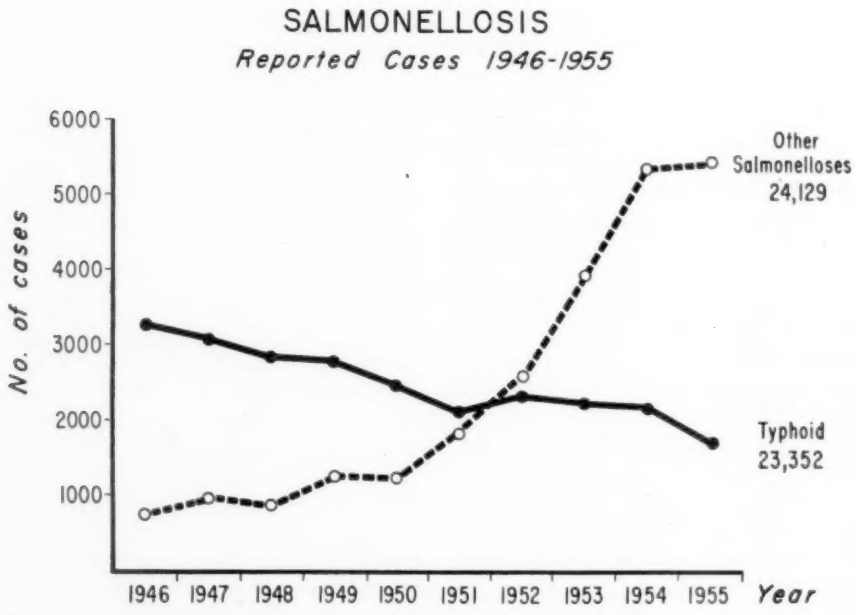

Fig. 1.—Total reported cases in the United States 1946 to 1955[2]

3) It is now recognized that a number of the oral antimicrobial agents are capable of producing a profound alteration in the composition of the bacterial population that normally inhabits the gastrointestinal tract. This by-product of antimicrobic therapy may be responsible for the superimposition of a serious infection on the one for which treatment was initially instituted. The organisms responsible for these superinfections are not necessarily drug-resistant variants of the microorganisms comprising the normal flora, but may be taxonomically different microbial species, which apparently cannot successfully compete with the customarily predominant normal flora. These increase in number and possibly in invasive capacity only after the normal flora has been eliminated or depressed by antimicrobial therapy. It is known that some coliform bacteria produce substances which suppress growth of salmonellae and which consequently may exert a protective role for the host against this group of pathogens (Levine *et al.*[7]). Furthermore, the majority of salmonella infections are cases of gastroenteritis, many of which are mild and recover spontaneously. However, if these should be treated with antibiotics that are ineffective against the salmonellae but are effective against the antagonizing organisms, it is conceivable that the intestinal flora may be so altered as to allow the salmonellae to grow luxuriantly and produce more severe infection. Salmonellae lurking in the bowel of a "carrier" have been reported as becoming "activated" as a result of prophylactic use of certain antibiotics (Finger and Wood[5]).

4) Cases of salmonellosis with focal manifestations have developed while patients have been on adrenal steroid therapy, suggesting that these hormones may in some manner contribute to dissemination of the organism from the portal of entry, in a way similar to that which has been observed in other infections (Weiss, Eisenberg and Flippin[13]).

The usual mode of human infection is by ingestion of contaminated food or drink, thus making the gastrointestinal tract the most frequent portal of entry. However, it has been shown that salmonellae may be transmitted to newborn infants in the delivery rooms via inhalation of the atmosphere contaminated by unsterile resuscitators. The observation that pleuropulmonary salmonellosis occurred in patients with diseased urinary tracts has led to the suggestion that the genitourinary tract could be a portal of entry, subsequent to ascending infection from the bowel (Weiss, Eisenberg and Flippin[13]). After gaining admission into the body, the organisms initiate an infection which may vary from a mild gastroenteritis to a severe blood stream disease with extra-intestinal localization, such as pneumonia. Experimental salmonella infections in humans have indicated that the variable host susceptibility and reactability, rather than the parasite, are responsible for the varied clinical manifestations ("Montevideo Doctrine") (Meyer[9]). However, some types of salmonellae seem much more likely to invade the blood stream than others. For example, *S. choleraesuis* is markedly invasive and carries the highest mortality (approximately 20%); whereas others, such as *S. enteritidis* rarely give rise to any illness other than transient irritation of the gastrointestinal tract (Saphra and Winter[11]).

It is well known that salmonellae frequently act as the "last straw" in persons whose resistance has been sapped by a pre-existing disease. However, a similar statement is applicable to many types of infections and is no way unique or peculiar to salmonellosis. Nevertheless, the development of

salmonella infections, particularly osteomyelitis, in patients with sickle-cell anemia does not appear to be a coincidence and may be due to several factors (Hook *et al.*[6]). Capillary thromboses in such cases may make the gastrointestinal tract less capable of resisting invasion by intestinal organisms, a situation that can be compared to the effect of gastrectomy (Waddell and Kunz[12]) in predisposing to salmonella infections. Also, debility and the frequent autosplenectomy in patients with sickle-cell anemia may decrease natural resistance to infection and predispose to invasion by salmonella organisms. Once salmonellae gain access to the blood stream, they may localize in areas of ischemia and necrosis caused by the sickling process. Ischemia of bone marrow may also lower focal resistance and permit the growth of dormant organisms. The effect of dual infections has long been noted in both animals and man. Calves infected with both salmonellae and another pathogen are more likely to die than if they had either infection alone. Likewise, in several other diseases there is strong evidence to indicate a specific predisposition to infection by salmonellae which far exceeds any general susceptibility to other bacterial species. These include malaria, relapsing fever, bartonellosis, and viral hepatitis (Bennett and Hook[1]). It has been pointed out that icterus is frequent in all of these disorders, including sickle-cell anemia. Severe impairment of liver function occurs in hepatitis and relapsing fever, and hemolysis and anemia characterize malaria, bartonellosis, and sickle-cell anemia (Bennett and Hook[1]).

Diagnosis. In view of the varied manifestations of salmonellosis, it has been suggested that signs and symptoms be classified into four clinical syndromes which would facilitate arriving at a clinical diagnosis. They are as follows: Gastroenterocolitis seen in approximately 67% of cases; septicemic or typhoidal syndrome, approximately 15%; focal manifestations, approximately 8%; or, an asymptomatic state marked only by laboratory evidence of salmonellae in the gastrointestinal tract, approximately 10%. These syndromes may occur individually, simultaneously, or consecutively during an infection; but, for the most part, there is nothing unique about salmonella infections. This is particularly true in cases with focal manifestations, in which the diagnosis is rarely made on clinical grounds, since most cases are regarded as having a Gram-positive coccal etiology until the cultural diagnosis is made. Many occur independently of previous symptoms of bacteremia or focalization may occur in the lungs during a typhoidal or septicemic syndrome. These cases are usually encountered sporadically without obvious relation to outbreaks of food poisoning and the localized infection often dominates the picture to the exclusion of intestinal manifestations. Although every salmonella serotype is capable of producing any or all of the protean manifestations of the disease, the majority of focal lesions are due to S. *choleraesuis*, S. *paratyphi hershfeldii*, and S. *typhimurium*.

As indicated, unequivocal proof of salmonella infection depends on the isolation and identification of the organism. However, bacteriologic diagnosis is often difficult because of lack of awareness of etiology or even impossible because of unjustified premature institution of antimicrobial therapy before collection of appropriate body fluid specimens for examination. The examination of blood serum for agglutinating antibodies often provides indirect evidence of infection, particularly when multiple studies demonstrate a significant rise or fall in titer of such antibodies. Antibody demonstration

also serves as further corroborative evidence in cases that yield positive cultures. The demonstration of a rise or fall in titer, at least of four-fold difference, is more meaningful diagnostically than the findings of a single determination (Eisenberg *et al.*[4]). However, in the presence of an appropriate history and clinical findings, a titer of 1:80 is considered suggestive; a titer of 1:160 or higher, under the same conditions, as diagnostic in patients with no previous history of immunization.

Although the serum agglutination provides presumptive evidence of infection due to salmonellae, it is impractical for the determination of serotype of infecting organism. The agglutination test is run against an array of antigens and the resulting antibody titers may indicate reactivity with one or more than one of the antigens in the array. All salmonellae possess at least two antigens which help to identify them serologically and which are capable of inducing the formation of serum agglutinins during infection. These are the "somatic" or "O" antigens, which are associated with the bacterial cell body and the "flagellar" or "H" antigens which are associated with the flagella of the organism. Theoretically, it should be possible to "pin-point" a salmonella serotype as being the agent responsible for infection by means of an appropriate battery of antigens used in examination of the serum. The practical necessity and desirability of this is highly questionable considering the fact that at least 200 varieties of salmonellae are known at present and for "type specific" identification of serum antibodies there would be required the use of a like, or even larger, number of antigens in the performance of a routine serodiagnostic laboratory procedure. The problems of preparing and maintaining such a large number of antigens is beyond the capabilities of most laboratories. From the standpoint of diagnostic requirement, all that is necessary is the detection of the largest variety of antibodies that are known to attend the most commonly occurring salmonella infections; this can be satisfied through the use of a small number of antigens (over 95% of the salmonellae isolated from infections in the United States are due to salmonellae from serogroups A, B, C_1, C_2, D, and E). Since only a few single antigens are type specific, the precise identification of a salmonella strain will require the identification of both "O" and "H" antigens of the recovered bacteria. This intricate and tedious technical procedure can be done best at a laboratory devoted entirely to such a procedure. Certainly, the identification and "finger-printing" of the numerous salmonellae is important from the clinical, epidemiologic, and statistical standpoints. Clinically, the isolation, identification, and typing help to establish the etiology of an enteric or parenteral disease, or both. This, in turn, leads to a definite prognostic and therapeutic approach in that certain types, for example S. *choleraesuis*, have a much more serious prognosis and consequently require a more active approach than other types, such as S. *tennessee* or S. *anatum*. Secondly, it helps the epidemiologist and public health officer to trace the source of infection and thus break the chain of transmission. Thirdly, the statistical data accumulated help to identify the more significant and more virulent types and thus serve as a guide in the choice of measures for control.

Treatment. For the most part, the treatment of salmonellosis with antimicrobial agents has been unsatisfactory. As indicated, there seem to be unique features in parasite-host relationship which set Salmonella organ-

isms apart from others producing acute infections in man. Also, there appears to be a puzzling disparity between *in vitro* sensitivity tests of salmonella and *in vivo* effectiveness of antimicrobial agents. It has been demonstrated experimentally that chloramphenicol and chlortetracycline at the same serum levels exerted comparable bacteriostatic effects upon *S. typhosa* but significantly large doses of the latter drug were required to achieve proper serum levels. This finding suggests that the differences in drug effectiveness in salmonellosis involve "drug-host," rather than "drug-parasite," relationship (Bennett and Hook[1]).

Data on *in vitro* susceptibility in our laboratory[4] indicate that of 62 different isolates tested, all were susceptible to chloramphenicol, while only 50% and 9.7% were sensitive to the tetracyclines and streptomycin, respectively. There did not appear to be an association between salmonella serotype and antibiotic susceptibility pattern. Others have demonstrated that virtually all strains of salmonella are inhibited by concentrations of chloramphenicol that are well within the range of serum levels attained *in vivo* by giving conventional doses of the drug. Also, many strains have been shown to be sensitive to kanamycin, polymyxin B, and neomycin. In addition, the administration of massive dosages of penicillin in conjunction with probenecid to promote serum levels of penicillin in excess of 16 units per ml. has proven effective in the treatment of certain types of salmonellosis (Rabe[10]).

Many cases of salmonella gastroenterocolitis are so mild and of such short duration they require no specific drug therapy. In those which are more severe or prolonged, chloramphenicol (0.5 gm.) orally every 6 hours may be tried. Certainly, protracted therapy should be discouraged since the resultant disturbances in enteric flora may precipitate a generalized infection or produce an undesirable toxic side effect.

The management of septic and typhoidal forms as well as focal manifestations of the disease is somewhat better defined. Chloramphenicol should be given in comparatively large doses (an initial loading dose of 2 gm. orally, followed by 1 gm. every 4 to 6 hours until defervescence has occurred); therapy is then continued with 1 gm. every 6 to 8 hours for an additional 10 to 20 days. Parenteral administration of chloramphenicol alone or in combination with the oral route is indicated in seriously ill patients, or in those unable to take the drug by mouth. The main reason for prolonged therapy is to reduce the risk of relapse, which occurs in an appreciable number of instances. Persistence of organisms in tissues and exudates is common, hence the importance of surgical drainage of suppurative processes. Relapses have been attributed to suppression of immunity by early intensive antibiotic therapy and for this reason several alternate regimens have been recommended. One procedure involves intermittent therapy in which "rest" periods of 3 to 4 days are interspersed with antibiotic administration for 5 days over a period of 3 to 4 weeks. The other is repeated intramuscular administration of an appropriate dead salmonella antigen to induce an early antibiotic response during antimicrobial therapy. In addition, cortisone, administered during the first 72 to 96 hours will frequently relieve the signs and symptoms of severe toxemia, although it may prove detrimental as far as perforation and bleeding of the bowel are concerned. The relative effectiveness of these various therapies remains to be evaluated by properly controlled studies.

One of the most thorny problems in the control of salmonellosis is the management of salmonella carriers. First of all, it is difficult to evaluate specific antimicrobial therapy in view of the highly variable periods of excretion of bacilli after intestinal infection. Most people who become salmonella carriers harbor the organism in their intestine or biliary passage for 30 to 60 days after onset of illness; this may be prolonged for a year and cease spontaneously or the carrier state may become permanent. Certainly, the antimicrobial agents have been disappointing in the treatment of chronic carriers. Hence, no useful purpose is served by subjecting such individuals to repeated courses of therapy. It seems more desirable to restrict their food handling activities. Cholecystectomy is indicated in chronic carriers with evidence of gallbladder disease. In contrast to the chronic carrier, apparent success has been observed in the treatment of convalescent carriers with chloramphenicol, kanamycin, polymyxin B, or neomycin. However, if the patient has harbored the organisms for over 4 months and is asymptomatic, it would seem best not to administer an antibiotic.

Summary and Conclusions. 1. Recent reports indicate that infections with salmonellae other than S. *typhosa* have been increasing steadily and markedly during the past few years. Possible explanations for this are suggested. The most interesting of these relates to our rapidly changing food habits (preparation, transportation, and dispensing) which afford a greater opportunity for food to be contaminated and larger numbers of persons to become infected with these organisms.

2. The fact that salmonellae frequently act as the "last straw" in persons whose resistance has been sapped by a pre-existing disease is in no way unique or peculiar to salmonellosis. Nevertheless, in several conditions there is strong evidence to indicate a specific predisposition to infection by salmonellae which appears to exceed any general susceptibility to other bacterial species; these include malaria, relapsing fever, bartonellosis, viral hepatitis, and sickle-cell anemia. An analogous susceptibility has been observed in patients who have had gastric surgery.

3. In most instances the clinical diagnosis of salmonellosis is difficult in that there is nothing unique about this infection, particularly in its focal manifestations. The latter cases are usually encountered sporadically without obvious relation to outbreaks of food poisoning and the localized infection often dominates the picture to the exclusion of intestinal manifestations.

4. The diagnosis of salmonellosis depends on the isolation and identification of the organism, although the examination of blood serum for agglutinating antibodies often provides indirect evidence of infection.

5. Although any one of several syndromes may be produced by the same or different salmonella serotypes, the majority of the more severe infections are due to S. *choleraesuis*, S. *paratyphi hershfeldii*, and S. *typhimurium*.

6. For the most part, the treatment of salmonellosis with antimicrobial agents has been disappointing. Chloramphenicol in the management of the septicemic, or typhoidal, and focal forms has been used successfully in a good number of cases. In salmonella gastroenterocolitis and carriers the antibiotics have proven of little or no value and one questions whether these drugs should be used in such cases.

7. Important steps in reducing the incidence of salmonellosis include: a) accurate bacterial diagnosis and reporting of cases; b) prompt epidemio-

logical follow-up; c) education of domestic and public food handlers in matters of personal hygiene; d) close supervision of abattoirs, food processing plants, and public eating places; e) isolation of salmonella carriers; f) discriminate use of antimicrobial agents; and, g) assessment of the need to include representative Group C organisms in the standard vaccine.

REFERENCES

1. **Bennett, I. L., Jr.,** and **Hook, H. W.:** Ann. Rev. Med., **10,** 1, 1959.
2. **Edwards, P. R.:** Ann. New York Acad. Sci., **70,** 598, 1958.
3. **Eisenberg, G. M., Palazzollo, A. J.,** and **Flippin, H. F.:** New England J. Med., **253,** 90, 1955.
4. **Eisenberg, G. M., Brodsky, L., Weiss, W.,** and **Flippin, H. F.:** Am. J. Med. Sci., **235,** 497, 1958.
5. **Finger, D.,** and **Wood, W. B.:** Am. J. Med., **18,** 839, 1955.
6. **Hook, E. W., Campbell, C. G., Weens, H. S.,** and **Cooper, G. R.:** New England J. Med., **257,** 403, 1957.
7. **Levine, M., Enright, J. R., Edgar, K. J., Shing, G. L.,** and **Tanimoto, R. H.:** Hawaii Med. J., **14,** 205, 1955.
8. **MacCready, R. A., Reardon, J. P.,** and **Saphra, I.:** New England J. Med., **256,** 1121, 1957.
9. **Meyer, K. F.:** Ibid., **249,** 804, 1953.
10. **Rabe, E. F.:** Pediatrics, **16,** 590, 1955.
11. **Saphra, I.,** and **Winter, J. W.:** New England J. Med., **256,** 1128, 1957.
12. **Waddell, W. R.,** and **Kunz, L. J.:** Ibid., **255,** 555, 1956.
13. **Weiss, W., Eisenberg, G. M.,** and **Flippin, H. F.:** Am. J. Med. Sci., **233,** 487, 1957.

SUMMARIO IN INTERLINGUA

Problemas Currente in Salmonellosis

1. Recente reportos indica que infectiones con salmonellas altere que *Salmonella typhosa* cresce in frequentia continue—e marcatemente depost plure annos. Explicationes possibile de iste phenomeno es presentate. Le plus interessante es le explication super le base del rapide alteration de nostre habitudes e costumes relative al alimentos (lor preparation, lor transporto, lor distribution, etc.), que ha resultate in plus extense occasiones pro le alimentos de contaminar se e pro plus grande numeros de personas de inficer se con iste organismos.

2. Le facto que salmonellas administra frequentemente le "colpo de gratia" a personas cuje resistentia es minate per le un o le altere morbo pre-existente non es un characteristica special de salmonellosis. Tamen, in plure conditiones pathologic on ha trovate forte indicationes que illos es associate con un predisposition a infectiones per salmonellas multo plus marcate que le predisposition general a infectiones per altere species bacterial. Tal conditiones es malaria, typho recurrente, bartonellosis, hepatitis virusal, e anemia a cellulas falciforme. Un susceptibilitate de character analoge ha essite notate in patientes subjicite a operationes gastric.

3. In le majoritate del casos le diagnose clinic de salmonellosis es difficile, proque il ha in iste infection nihil que es unic, particularmente in su manifestationes focal. Casos characterisate per manifestationes focal es usualmente incontrate como occurrentias sporadic sin relation evidente con eruptiones de intoxication alimentari, e le infection localisate predomina frequentemente in le tableau clinic usque al exclusion total del manifestationes intestinal.

4. Le diagnose de salmonellosis depende del isolation e identification del organismo, sed le studio del sero sanguinee pro le presentia de anticorpore agglutinante produce frequentemente un prova indirecte del infection.

5. Ben que le un o le altere de plure syndromes pote esser producite per le mesme serotypo, le majoritate del plus sever infectiones es causate per S. *choleræsuis*, S. *paratyphi hershfeldii*, e S. *typhimurium*.

6. A generalmente parlar, le tractamento de salmonellosis con agentes antimicrobial ha remanite disappunctante. In le tractamento de un numero considerabile del formas septicemic (o typhoide) e focal, chloramphenicol esseva usate a bon successo. In gastroenterocolitis per salmonella e in le tractamento de vectores, le antibioticos se ha provate de pauc o nulle valor, e on pote demander se si iste drogas non deberea esser abandonate como medication in tali situationes.

7. Le sequentes es importante mesuras in reducer le incidentia de salmonellosis: (a) accurate diagnoses bacterial e registration del casos; (b) prompte observationes epidemiologic sequential; (c) education de manipulatores domestic e public de alimentos con respecto al principios del hygiene personal; (d) un stricte controlo de abattitorios, fabricas de processage de alimentos, e locales de consumption public de alimentos; (e) isolation de vectores de salmonella; (f) le uso circumspecte de agentes antimicrobial; e (g) le studio del necessitate de includer organismos representative del Gruppo C in le vaccino standard.

SUMMARIO IN INTERLINGUA

(See page 307 for original article)

Mortes Respiratori e Cardiac Occurrente a Los Angeles sub Conditiones de Smog in 1956, 1957, e 1958

Le autor porta al currente su previe studios del mortalitate respiratori e cardiac in smog a ozono a Los Angeles (vide iste periodico, **223**, 379, 1957). Ille verifica le occurrentia de quasi 400 mortes per anno que es correlationate con smog in le Contato de Los Angeles. In plus, ille establi un relation directe e intime inter le maximos diurne del temperatura e le formation de ozono (o oxydante) in le atmosphera de ille region. Iste stricte relation inter ozone e temperatura existe durante le tres annos ab 1956 ad 1958 a temperaturas inter 46 e 104 F. Es signalate que le excesso de mortes occurrente in dies con smog non pote logicamente esser considerate como mortes causate per le calor, excepte quando le temperatura es supra 96 F (viste le basse humiditate de Los Angeles), e que per consequente il pare justificate concluder definitemente que smog a ozono (o oxydante) representa un hasardo sanitari pro le communitate a nivellos de ozono de plus que 0,1 ppm. Es notate que le objectivo de prevenir nivellos atmospheric de ozono de plus que 0,1 ppm il esserea necessari reducer le non-comburite hydrocarburos in le gases de escappamento del automobiles (que es le fonte major de preformatores de ozono) per circa 85 a 90 pro cento ab le nivellos nunc in existentia. Es presentate tabulas monstrante pro tres annos le maximos diurne de temperatura, le cifras diurne de mortalitate respiratori e cardiac, e le valores medie del maximos diurne del concentrationes de ozono (o oxydante) ab omne le reportante stationes in le Contato de Los Angeles.

COMPARATIVE ACTIVITY OF FOUR TETRACYCLINE ANALOGUES AGAINST PATHOGENIC BACTERIA *IN VITRO*[*]

By Hans A. Hirsch, M.D.
RESEARCH FELLOW IN MEDICINE, THORNDIKE MEMORIAL LABORATORY AND HARVARD MEDICAL SCHOOL

AND

Maxwell Finland, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; ASSOCIATE DIRECTOR, THORNDIKE MEMORIAL LABORATORY, AND PHYSICIAN-IN-CHIEF, FOURTH MEDICAL SERVICE, BOSTON CITY HOSPITAL, BOSTON, MASSACHUSETTS

WITH THE TECHNICAL ASSISTANCE OF

Clare Wilcox

(From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services, Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts)

In 1957, McCormick *et al.*[5] described a new family of compounds related to the tetracyclines; two of them, namely 6-demethyltetracycline and 7-chloro-6-demethyltetracycline, were produced by a mutant strain of *Streptomyces aureofaciens* (Duggar *et al.*[1]), from which chlortetracycline (Aureomycin) was originally produced. The 2 new demethylated antibiotics were found to be highly resistant to degradation by acid or alkali and to have about the same activity as their respective methylated analogues. Previous studies carried out by Sweeney *et al.*[6] with 7-chloro-6-demethyltetracycline, now given the generic name demethylchlortetracycline (DMCT), indicated that oral administration in human beings yielded more sustained levels of this antibiotic in the blood as compared with either tetracycline (TC) or chlortetracycline (CTC). In this laboratory it was also shown that DMCT produces higher and more sustained levels of antibacterial activity in the blood of normal individuals than similar single doses of CTC, TC or oxytetracycline (OTC) (Hirsch and Finland[2], Kunin and Finland[4]), and as compared with TC when administered in 2 doses daily of similar amounts (Kunin and Finland[4]).

The present study reports a comparison of the activity of the 4 tetracycline analogues against human pathogenic bacteria *in vitro*. The strains were tested with these analogues simultaneously on the surface of agar plates, in which the antibiotics were incorporated in 2-fold dilutions. Blood agar was used for pneumococci and streptococci and "chocolate" agar for *H. influenzae* and Neisseria. Inhibition was recorded after 24 hours incubation at 37° except for the Neisseria which were incubated for 48 hours.

Results. The susceptibility of 861 strains of 15 different genera or species of human pathogenic bacteria to the 4 analogues is summarized in Table 1. Differences in activity of the individ-

[*]Aided by a grant (E-23) from the National Institutes of Health.

ual analogues against the various strains of the different organisms are noted, but these, in general, were not very striking. This table, however, does not show differences in activity of the different analogues against individual strains. This is summarized in Table 2 which lists the proportion of strains of each genus or species which were most susceptible to one or another of the analogues. The italics indicate the analogue with the highest proportion of strains against which it was the most active.

Another comparison based on comparative ratings of the antibiotics is given in Table 2. In rating the activity of the different analogues against each strain, the most active was rated as 1 and the others compared with it essentially in terms of the number of 2-fold higher concentrations required for inhibition of that strain. When growth of a strain was completely inhibited in one concentration and markedly but incompletely inhibited in the next greater concentration, a value of ½ was added to the rating of the latter antibiotic.

From the data presented it is seen that DMCT was the most active against the greater proportion of strains of most of the species and genera listed, but CTC was more active against some of the Gram-positive organisms. TC was the most active only against the "resistant" staphylococci and OTC was the most active against some of the species of Gram-negative organisms. Of all the organisms tested with all 4 analogues, DMCT was the most active, or as active as any other, against about two-thirds of all strains, whereas TC was the most active against about one-half of the strains classified as "resistant." The difference in the average ratings were not very large, but individual strains differed up to 4- or 8-fold in activity.

Comparisons of DMCT with each of the other 3 tetracycline analogues individually are shown in Table 3. Here the comparative activity of the different analogues against strains of the various genera and species are shown more clearly. Thus, as compared with CTC, DMCT was more active against the majority of all strains tested, although both appeared to be similar in activity against "resistant" strains Among most of the individual genera and species, DMCT was the more active of the two, but CTC was more active against a greater proportion of strains of "resistant" S. *aureus* and of all varieties of streptococci, and the two were essentially equal in activity against sensitive strains of S. *aureus* and resistant strains of *E. coli*.

As compared with OTC also, DMCT appeared to be equally active against 45% of the strains tested but it was more active against most of the others. However, OTC was more active against more strains of pneumococci, meningococci, "sensitive" *E. coli* and Pseudomonas. Both were essentially similar in activity against strains of Klebsiella, Aerobacter, Shigella and all varieties of streptococci except "sensitive" enterococci; most of the latter were more susceptible to DMCT.

Likewise, as compared with TC, DMCT appeared to be the more active against the majority of all strains tested, and this was true of most of the genera and species except for the resistant strains of S. *aureus*, the great majority of which required less TC to produce inhibition of growth. Both of these antibiotics, however, were essentially similar in activity against strains of pneumococci, hemolytic streptococci, *Str. viridans*, meningococci, *E. coli* and Pseudomonas.

Discussion. Previous studies have shown that DMCT produces more sustained levels of antibacterial activity in the blood than any of the other 3

TABLE 1.—SUSCEPTIBILITY OF 861 STRAINS OF VARIOUS BACTERIA TO TETRACYCLINE ANALOGUES

Organism	Number of Strains	Antibiotic	Minimum Inhibiting Concentration, μg./ml. Percent of Strains ≦ 0.05	0.1	0.2	0.4	0.8	1.6	3.1	6.3	12.5	25	50	100	>100	M.I.C. ≧ 2/3 of Strains
D. pneumoniae	25	OTC			36	48	16									.4
	25	TC			8	64	28									.4
	25	CTC			56	36	8									.4
	25	DMCT			8	64	28									.4
Str. pyogenes	17	OTC				41	23	23	6	6						1.6
	17	TC			6	30	41	12	6	0	0	6				.8
	17	CTC			18	18	47	6	6	0	0	0	6			.8
	17	DMCT			18	12	53	12	0	0	0	0	6			.8
Str. viridans	20	OTC					20	65	5	5	5					1.6
	20	TC				5	35	20	25	10	0	5				1.6
	20	CTC				5	65	10	15	0	5					.8
	20	DMCT				10	35	15	35	0	5					3.1
Enterococcus	50	OTC					2	22	14	6	0	6	24	10	16	50
	50	TC					0	16	24	0	0	2	10	28	20	100
	50	CTC					4	32	4	0	6	22	10	8	14	25
	50	DMCT					4	24	10	2	0	16	14	16	14	50
Staph. aureus	125	OTC				1.6	19.2	30.4	5.6	0.8	0	1.6	0.8	0	40.0	>100
	253	TC				0.4	22 5	28.1	5.5	1.6	1.6	2.0	26.1	11.9	0.4	50
	125	CTC				19.2	14.4	16.8	4.0	3.2	4.0	0.8	2.4	24.8	10.4	100
	253	DMCT			0.8	15.0	28.5	11.1	2.4	0.4	1.6	2.0	1.2	19.0	18.2	100
	100	DMT						23	22	1	1	2	3	1	47	>100
N. gonorrhoeae	132	OTC	1.5	11.4	34.8	44.7	6.1	1.5								.4
	132	TC	0.8	7.6	30.3	45.5	14.4	1.5								.4
	132	CTC	2.3	4.5	18.2	41.7	26.5	5.3	1.5							.4
	132	DMCT	5.3	20.5	39.4	31.8	3.0									.2
N. meningitidis	15	OTC				20	73	7								.8
	15	TC				7	60	33								.8
	15	CTC				7	27	67								1.6
	15	DMCT				33	27	40								.8

H. influenzae	50	OTC	2	34	45	10					3.1
	50	TC		54	44	2					3.1
	50	CTC		20	76	4					3.1
	50	DMCT	18	60	22						1.6
Salmonella	19	OTC			47	47	0	0	0	5	6.3
	19	TC			32	63	0	0	0	5	6.3
	19	CTC			11	68	16	0	5		6.3
	19	DMCT		5	84	5	0	0	0	5	3.1
Shigella	30	OTC		67	27	0	0	0	0	0	7	1.6
	30	TC		17	73	3	0	0	0	0	7	3.1
	30	CTC		13	63	17	0	0	0	0	7	3.1
	30	DMCT		57	37	0	0	0	0	3	3	3.1
Esch. coli	80	OTC		40	26	13	4	0	1	0	16	6.3
	80	TC		3	63	13	4	3	4	1	11	6.3
	80	CTC		4	18	30	21	3	1	4	11	12.5
	80	DMCT		10	49	16	6	3	3	0	14	6.3
K. pneumoniae	74	OTC	4	21	42	27	4	1				3.1
	74	TC		14	35	40	10	1				6.3
	74	CTC		4	18	54	15	8	1			6.3
	74	DMCT	4	22	57	14	3	1				3.1
Aerobacter	40	OTC			20	50	20	3	0	0	8	6.3
	40	TC			8	33	43	10	0	3	5	12.5
	40	CTC			5	30	40	15	5	3	3	12.5
	40	DMCT			20	53	20	0	0	3	5	6.3
Proteus	32	OTC			3	0	6	0	6	0	84	>100
	32	TC			3	0	6	3	16	25	47	>100
	32	CTC			3	6	0	0	0	6	84	>100
	32	DMCT			3	6	0	6	38	22	25	100
Ps. aeruginosa	24	OTC							50	46	4	100
	24	TC							4	67	29	100
	24	CTC							0	4	96	>100
	24	DMCT							4	79	17	100

OTC = oxytetracycline; TC = tetracycline; CTC = chlortetracycline; DMCT = demethylchlortetracycline; DMT = demethyltetracycline. M.I.C. = minimum inhibiting concentration.

TABLE 2.—RELATIVE *IN VITRO* ACTIVITY OF 4 TETRACYCLINE ANALOGUES

*Organism**	*No. of Strains Tested*	*Most Active-Antibiotic*				*Average Activity Rating*†				*Range of M.I.C. of Most Active*
		OTC	*TC*	*CTC*	*DMCT*	*OTC*	*TC*	*CTC*	*DMCT*	
Staph. aureus		Percent of Strains								*μg. per ml.*
Series A: Sensitive	53	30	19	58	*72*‡	2.0	2.0	1.5	*1.3*‡	0.4–12.5
Resistant	47	0	*100*	6	0	2.9	*1.0*	2.2	2.6	50 –100
Series B: Sensitive	82	—	23	—	*96*	—	1.7	—	*1.1*	0.4–25
Resistant	46	—	98	—	35	—	*1.0*	—	1.8	50 –100
Series C: Sensitive	25	12	12	*84*	52	2.0	2.0	1.2	1.4	0.2–25
D. pneumoniae	25	36	16	*84*	20	1.5	1.8	*1.2*	1.7	0.2–0.8
Str. pyogenes	17	29	41	*76*	47	1.7	1.6	*1.4*	1.5	0.2–6.3
Enterococcus: Sensitive	35	6	0	83	43	2.0	2.3	*1.1*	1.6	0.8–25
Resistant	15	33	13	*40*	33	1.6	2.0	*1.5*	1.6	50 –>100
Str. viridans	20	25	35	*70*	45	1.9	2.0	*1.3*	1.8	0.4–12.5
N. gonorrhoeae	132	41	21	14	88	1.5	1.8	2.2	*1.1*	0.03–0.8
N. meningitidis	15	73	33	0	40	*1.2*	1.5	1.9	1.4	0.4–0.8
H. influenzae	50	34	38	16	*90*	1.7	1.7	1.9	*1.1*	0.8–3.1
K. pneumoniae	74	49	19	5	*74*	1.5	1.8	2.3	*1.2*	0.8–25
E. coli: Sensitive	67	79	24	13	34	*1.2*	1.6	2.2	1.6	1.5–12.5
Resistant	13	0	*31*	15	15	2.0.	*1.6*	1.8	1.8	50 –>100
Aerobacter: Sensitive	37	51	14	16	*68*	1.4	1.9	2.0	*1.3*	3.1–12.5
Resistant	3					2.3	2.0	*1.3*	2.0	50 –>100
Salmonella: Sensitive	18	50	28	6	*100*	1.3	1.4	1.8	*1.0*	1.5–6.3
Resistant	1					2	2	2	1	50
Shigella: Sensitive	28	*64*	5	1	46	*1.2*	1.7	1.9	1.4	1.5–3.1
Resistant	2					2.0	2.0	2.0	*1.5*	100 –>100
Proteus: Sensitive	4					2.1	1.8	1.8	*1.5*	3.1–25
Resistant	28	4	18	4	*61*	2.4	1.9	2.4	*1.5*	50 –>100
Ps. aeruginosa: Resistant	24	*96*	29	4	33	*1.0*	1.5	2.3	1.5	50 –>100
All Strains excluding *Staph. aureus* Series B:										
Sensitive	600	44	21	29	*65*	1.6	1.8	1.9	*1.3*	≤25
Resistant	133	22	*49*	11	25	2.2	*1.5*	2.1	1.9	>50

Abbreviations: OTC = oxytetracycline; TC = tetracycline; CTC = chlortetracycline; DMCT = demethylchlortetracycline; M.I.C. = minimum complete inhibiting concentration.

**Staph. aureus:* Series A—Randomly selected strains tested with all 4 analogues + demethyltetracycline (DMT); none of these were more sensitive to DMT and av. rating for latter was 2.5 for "sensitive" and 2.9 for "resistant" strains. Series B = consecutive strains selected and tested only with TC and DMCT; Series C = consecutive strains selected on basis of wide zone in disc-sensitivity test with tetracycline.

The following strains were obtained from Dr. P. R. Edwards, Communicable Diseases Center, U.S.P.H.S., Atlanta, Ga.: *K pneumoniae* representative of all 73 types; *E. coli,* 10 strains of each of 8 "pathogenic" types, "O-B-" series; Aerobacter, 20 strains each of *A. aerogenes* and *A. cloacae.* All other strains had been recently isolated from infected sources at this hospital.

"Sensitive" includes strains for which M.I.C. of most active analogues was ≤25 μg. per ml.; "Resistant" strains were those for which M.I.C. of the most active analogue was ≥50 μg. per ml.

†Rating based on a value of 1 for the most active analogue (lowest M.I.C.); 2 × lowest M.I.C. = 2; 4 × lowest M.I.C. = 3 etc.

‡Italicized numbers indicate the value for most active analogue; in the percentage columns the totals are >100% because more than one antibiotic was equally active against some strains.

previously available tetracycline analogues (Hirsch and Finland[2], Kunin, Dornbush and Finland[3], Kunin and Finland[4], Sweeney *et al.*[6]). This was shown to be due to the slower renal excretion and greater stability of DMCT (Kunin, Dornbush and Finland[3]). When compared on the basis of antibacterial activity calculated in comparison with the same standard assay organisms and any one of the 4 analogues, DMCT also produced much greater activity than any of the other analogues, particularly after the first 3 hours; the differences, based on single oral doses given to the same individuals, have averaged at least 3-fold, and in some instances up to 8-fold or more, particularly as compared with OTC (Hirsch and Finland[2]).

The comparisons cited, however, have been made chiefly with standard assay organisms; *S. lutea* generally was employed, but strains of *Str. hemolyticus* and *S. aureus* were also used and these were all more susceptible to DMCT. The data presented here show that DMCT is also at least as active

TABLE 3.—COMPARISON OF *IN VITRO* ACTIVITY OF DEMETHYLCHLORTETRACYCLINE (DMCT) WITH THAT OF CHLORTETRACYCLINE (CTC), OXYTETRACYCLINE (OTC) AND TETRACYCLINE (TC)

		DMCT cf. CTC			*DMCT cf. OTC*			*DMCT cf. TC*		
			More Active			*More Active*			*More Active*	
Organism*	*Number of* Strains§	=	CTC	DMCT	=	*OTC*	*DMCT*	=	*TC*	*DMCT*
					Percent of Strains					
S. aureus, S	160^{77}	51	21	29	35	8	57	26	5	69
R	93^{48}	48	46	6	63	0	38	18	82	0
D. pneumoniae	25	28	4	78	52	40	8	64	12	24
Str. pyogenes	17	47	35	18	29	29	41	30	30	41
Str. viridans	20	45	45	10	25	35	40	30	30	40
Enterococcus, S	33	30	55	15	27	9	64	9	6	85
R	17	35	41	25	53	24	24	65	6	29
N. gonorrhoeae	132	17	3	80	35	10	55	25	3	72
N. meningitidis	15	53	0	47	27	47	27	33	27	40
H. influenzae	50	22	0	78	42	0	58	28	10	62
E. coli, S	67	40	4	56	37	54	9	51	24	25
R	13	77	15	8	85	0	15	85	15	0
Klebsiella	74	14	0	86	59	15	26	16	10	74
Aerobacter, S	37	27	8	65	49	27	24	22	8	70
R	3	*1*†	*2*		*2*		*1*	*1*	*1*	*1*
Shigella, S	28	25	7	68	54	29	17	32	7	61
R	2	*1*		*1*	*1*		*1*		*1*	*1*
Salmonella, S	18	11	0	89	50	0	50	28	0	72
R	1		*1*		*1*			*1*		
Proteus, S	4	*1*	*1*	*2*	*1*		*3*	*1*		*3*
R	28	32	0	68	36	0	64	36	11	54
Pseudomonas, R	24	17	0	83	50	50	0	58	13	29
All "sensitive"	680^{597}	29	11	61	41	19	40	28	10	62
All "resistant"	181^{136}	40	25	35	56	12	32	36	48	16
Total	861^{733}	31	13	56	43	18	39	30	18	52

*S = sensitive (M.I.C. ≤25 μg. per ml.) and R = resistant (M.I.C. ≥50 μg. per ml.) for the more active analogue.

§All strains were tested with DMCT and TC; superscripts indicate numbers excluding those not tested with CTC and OTC (83 sensitive and 45 resistant strains of *S. aureus*).

†Italics indicate number of strains rather than percent.

as any of the other analogues and more active than all of them against the majority of strains of most of the common pathogenic organisms encountered clinically. This, coupled with the longer sustained and generally higher blood levels of DMCT, suggest that it should be superior to the other analogues at least in activity. It also suggests that similar clinical effects may be expected from substantially smaller doses of DMCT and also that doses may be given at less frequent intervals. Limited experience in this clinic to date appears to substantiate this, and the lower doses have been accompanied by fewer gastrointestinal side-effects. More experience, however, will be required before this can be firmly established.

Conclusions. On the basis of simultaneously performed tests of *in vitro* susceptibility of a large number of strains of various human pathogenic bacteria, demethylchlortetracycline appears to be generally more active than any of the other 3 tetracycline analogues now available.

REFERENCES

1. **Duggar, B. M.,** and **42 Others:** Ann. New York Acad. Sci., **51,** 175, 1948.
2. **Hirsch, H. A.,** and **Finland, M.:** New England J. Med., **260,** 1099, 1959.
3. **Kunin, C. M., Dornbush, A. C.,** and **Finland, M.:** J. Clin. Invest., **38,** 1950, 1959.
4. **Kunin, C. M.,** and **Finland, M.:** New England J. Med., **259,** 999, 1958.
5. **McCormick, J. R. D., Sjolander, N. O., Hirsch, U., Jensen, E. R.,** and **Doerschuk, A. P.:** J. Am. Chem. Soc., **79,** 4561, 1957.
6. **Sweeney, W. M., Hardy, S. M., Dornbush, A. C.,** and **Ruegsegger, J. M.:** Antibiotics & Chemother., **9,** 13, 1959.

SUMMARIO IN INTERLINGUA

Comparation de Quatro Analogos Tetracyclinic in Lor Activitate in Vitro Contra Bacterios Pathogenic

Super le base de simultaneemente effectuate tests del susceptibilitate in vitro de grande numeros de racias de varie bacterios pathogene human, il pare que demethylchlortetracyclina es generalmente plus active que ulle del altere 3 analogos tetracyclinic que es currentemente disponibile.

VIBRATORY SENSE AND OSCILLOMETRIC INDEX IN GOUT AND IN RHEUMATOID ARTHRITIS*

By T. S. Danowski, M.D.
PROFESSOR OF RESEARCH MEDICINE

Campbell Moses, Jr., M.D.
ASSOCIATE PROFESSOR OF MEDICINE

AND

Harry M. Margolis, M.D.
ASSISTANT PROFESSOR OF MEDICINE

(From the University of Pittsburgh School of Medicine, the Addison H. Gibson Laboratory, the Falk Clinic and the Medical Center, Shadyside, Montefiore, and St. Margaret's Hospitals, Pittsburgh, Pennsylvania)

The view has been expressed that patients with gout, like those with diabetes mellitus, are more susceptible to the so-called degenerative disorders such as arteriosclerosis (Kohn and Prozan[6]), but only gouty nephropathy is well-recognized. Neither have there been any well-documented descriptions of neuropathy as a feature of gout.

In rheumatoid arthritis on the other hand the blood pressure may be abnormal (Turner and Lansbury[7]), the possibility of a higher incidence of heart disease has been raised (Bradfield and Hejtmancik[1], Coste and Deshayes[2], Cruickshank[3]), and necrotizing arteriolitis or vasculitis can occur (Kemper, Baggenstoss and Slocumb[5]). Also, occasional examples of peripheral neuritis, perivascular inflammatory nodules of the perineurium and neural and neuronal degeneration have been described (Irby, Adams and Toone[4]).

This report establishes that the threshold for the perception of vibrations is often increased in gout and in rheumatoid arthritis but that oscillometric readings are grossly normal in both entities.

Material and Methods. An electric vibrator (Biothesiometer) in which the rate of movement of a metal rod capped by a plastic disc could be reproducibly varied by increasing the input of current was used. The initial perception of vibration was recorded at nine points on both sides of the body (external and internal condyles, radius, ulna, ilium, patella, external and internal malleoli, and great toe) in control subjects and in patients under treatment for gout or rheumatoid arthritis.

Oscillometric readings were obtained from the upper arm, forearm, mid-thigh, and mid-leg on both sides of the body.

The medical histories of the patients were reviewed for past and current therapy. All of the gout patients were taking colchicine (usually grain 1/100th) and Benemid (usually 1.5 gm.) each day. Virtually all of the arthritics had received or were receiving adrenocortical type steroids in addition to variable regimens of physiotherapy, gold salts, phenylbutazone, and others.

Control data on the threshold for vibration perception and oscillometric readings in males and females in the various age groups are available from measurements on apparently healthy adults who were inmates of the

*Aided by grants from the Western Pennsylvania Chapter of the Arthritis and Rheumatism Foundation and the John A. Hartford Foundation. This study is a facet of the Greater Pittsburgh Plan for the Control of Heart Disease.

Western Penitentiary or employees of the University of Pittsburgh or of a local department store.

Results. The findings are presented in Figs. 1 through 5. Sites of the most pronounced differences have been selected for illustration.

From Fig. 1 it is evident that the patients with gout compared to controls had a higher threshold for perception of vibrations. The mean electric vibrator reading for the gouty subjects was 29 ± 12 and for the controls 14 ± 8. This difference is statistically significant with a p value of >0.001. No significant difference was noted in the oscillometric readings of control and gouty subjects; the mean oscillometric index of control subjects was 4.3 ± 2 and of those with gout 3.1 ± 1 (Fig. 2).

A similar rise in vibratory sense threshold was observed in both males and females with rheumatoid arthritis (Fig. 3). The mean vibrator reading for the male arthritis patients was 23 ± 11 and for the female 22 ± 11 with the male controls having readings of 14 ± 7 and the females 10 ± 4. These differences are also statistically significant (p = >0.001). The mean oscillometric index in males and females with arthritis (Fig. 4) was 3.4 ± 1 and 3.1 ± 1, respectively, compared to mean values of 4.3 ± 2 in male controls and 3.1 ± 1 in the females. These are not statistically significant differences.

In Fig. 5 the duration of the rheumatoid arthritis has been plotted against the threshold for the perception of vibrations at the internal malleolus. It may be seen that the majority of the readings above 30 were found in patients in whom arthritis had been present for less than 10 years.

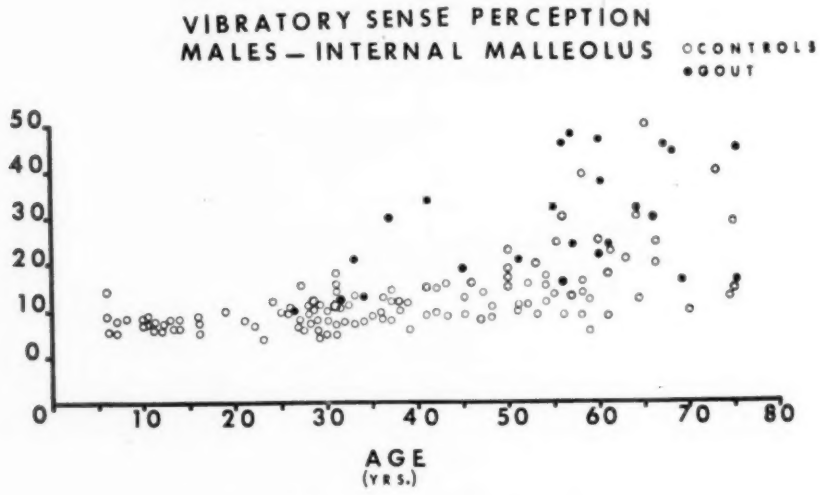

Fig. 1.—Vibratory sense measurements in gout.

Patients with gout have a higher threshold for perception and vibratory movements compared to control subjects in the same age group.

	Mean	±	*S.D.*	*(N)*
Gout	29	±	12	(24)
Controls	14	±	8	(94)

This difference is statistically significant.

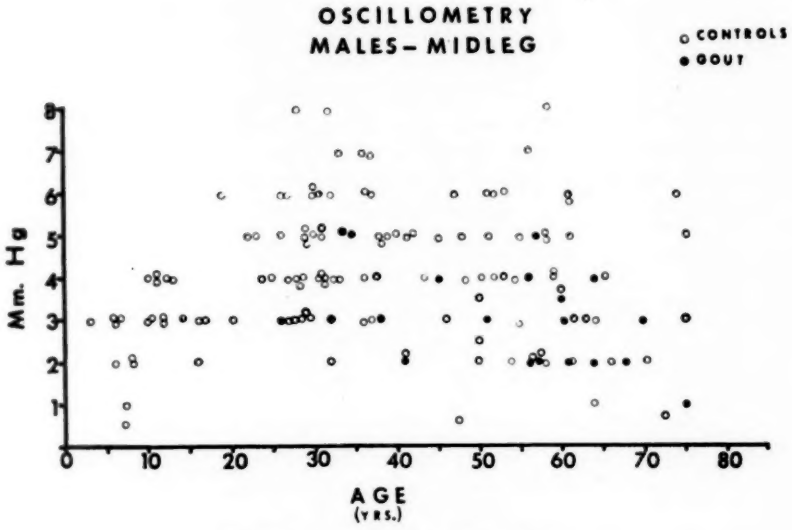

Fig. 2.—Oscillometric index in gout.

The mean oscillometric index in gouty patients was 3.1 and in control subjects was 4.3. This difference is not significant.

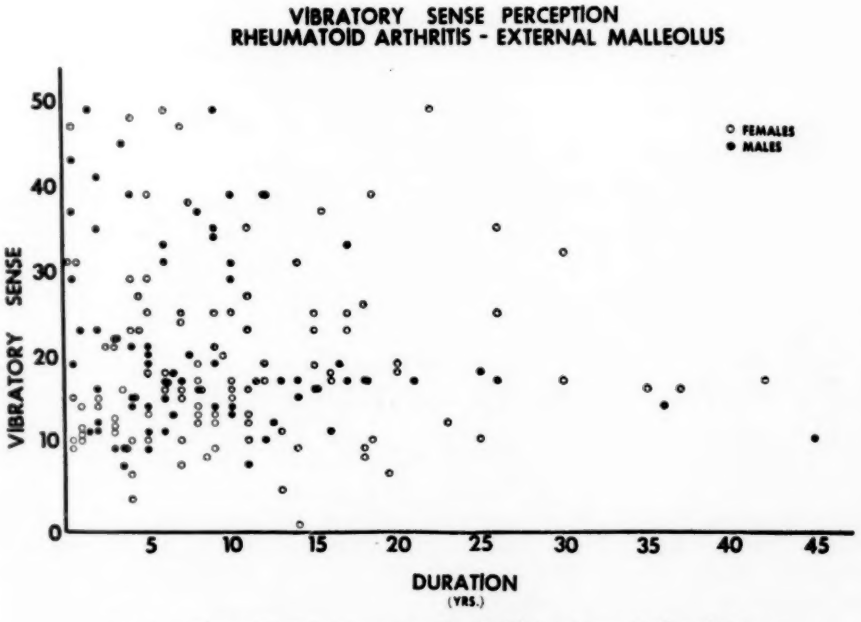

Fig. 3.—Elevated vibratory sense threshold in rheumatoid arthritis.

The mean reading in the male arthritic patients was 23 ± 11 (70), and in females 22 ± 11 (125). The readings on the controls were 14 ± 7 (101) and 10 ± 4 (102) in males and females, respectively. These differences are statistically significant.

Similar evaluation of the patients with gout revealed that an elevated threshold for vibration perception was encountered in patients whose gout could be traced back 2 to 23 years.

Discussion. These findings provide further support for the general impression that gouty patients have an increased susceptibility to so-called degenerative diseases and indicate that diminished vibratory sense acuity may have to be included in the spectrum of possible changes. The origins of this abnormality in gout and its relationship, if any, to the hyperuricemia or to the deposition of urates is not established. Although it may fall into the category of a degenerative disorder, the neuropathy could be related to vitamin deficiencies induced perhaps by the therapy currently employed. For example, it is conceivable that the uricosuric agents also increase the urinary losses of vitamins. This possibility is now being tested.

In rheumatoid arthritis the finding of elevated vibratory sense thresholds is in keeping with the knowledge that neuropathy may occur in this entity but the mechanism of this neurop-

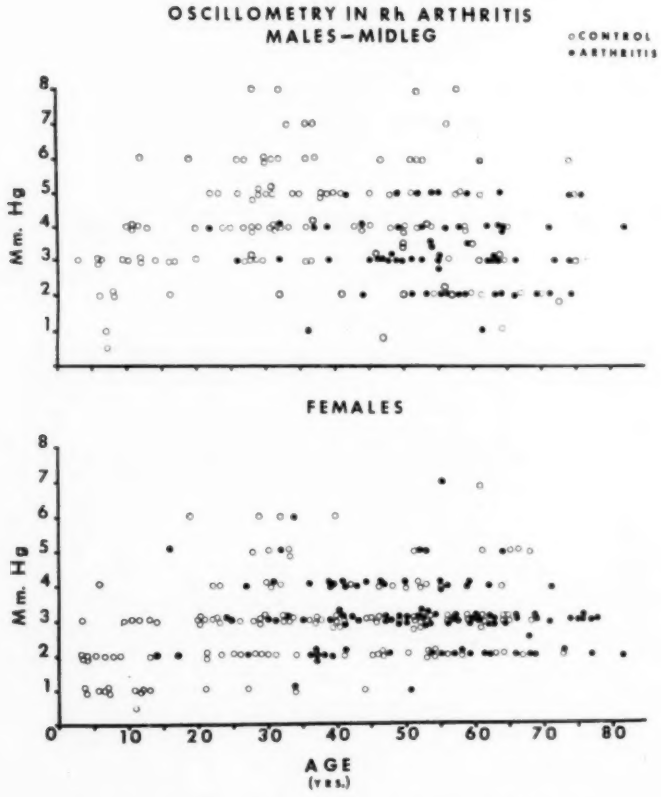

Fig. 4.—Oscillometric readings in rheumatoid arthritis.

In male arthritics 3.4 ± 1 (67) vs. 4.3 ± 2 (101) in male controls; in female arthritics, 3.1 ± 1 (112) compared to 3.1 ± 1 (103) in female controls.

athy is not established. Several workers have suggested that vascular changes of the necrotizing vasculitis type are produced or intensified in arthritics by adrenocortical steroid therapy. Review of the therapeutic regimens employed in our arthritic patients to determine whether adrenocortical steroids played a role in either the changed level of vibration perception or of oscillometric readings proved inconclusive because virtually all had recently received or were receiving these agents.

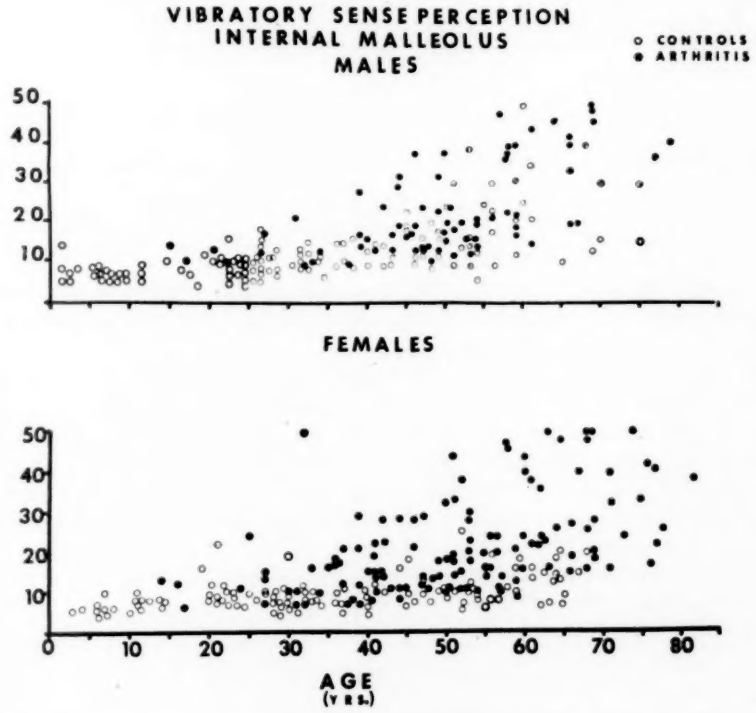

Fig. 5.—Vibratory sense perception in relationship to duration of rheumatoid arthritis.

The majority of the readings above 30 were obtained in patients in whom arthritis had been present for 10 years or less.

Summary and Conclusions. (1) Patients with gout or rheumatoid arthritis undergoing conventional modern treatment were found to have significantly increased thresholds for vibratory sense perception.

(2) The origins of the decreased acuity of vibratory sense in gout are not established and the possibility of vitamin deficiency secondary to therapy with uricosuric agents has not been excluded.

(3) Neither is a clear explanation available for the increased threshold for the perception of vibration in rheumatoid arthritis, though it is recognized that neuropathy may be a feature of this disorder. Our observations do not permit evaluation of the possibility that adrenocortical steroid therapy played a role in the vibratory sense

abnormalities, as it may in the necrotizing vasculitis occasionally seen in rheumatoid arthritis.

(4) The oscillometric index was grossly normal in both the gouty and the arthritic patients.

REFERENCES

1. **Bradfield, J. Y.,** and **Hejtmancik, M. R.:** Arch. Int. Med., **86,** 1, 1950.
2. **Coste, F.,** and **Deshayes, P.:** Rev. Rheum., **25,** 697, 1958.
3. **Cruickshank, B.:** J. Path. & Bact., **76,** 223, 1958.
4. **Irby, R., Adams, R. A.,** and **Toone, E. C., Jr.:** Arthritis and Rheumatism, **1,** 44, 1958.
5. **Kemper, J. W., Baggenstoss, A. H.,** and **Slocumb, C. H.:** Ann. Int. Med., **46,** 831, 1957.
6. **Kohn, P. M.,** and **Prozan G. B.:** J. Am. Med. Assn., **170,** 1909, 1959.
7. **Turner, L. W.,** and **Lansbury, J.:** Am. J. Med. Sci., **227,** 503, 1954.

SUMMARIO IN INTERLINGUA

Le Senso Vibratori e le Indice Oscillometric in Gutta e in Arthritis Rheumatoide

1. Esseva constatate que patientes con gutta o con arthritis rheumatoide sub typic tractamento moderne ha significativemente elevate valores pro le limine del perception sensori de vibrationes.

2. Le origine del reducite acuitate del senso vibratori in gutta non es cognoscite. Le possibilitate de un deficientia de vitaminas secundari al therapia con agentes uricosuric non pote esser excludite.

3. Similemente il non existe a iste tempore un explication clar del elevate limine del perception de vibrationes in subjectos con arthritis rheumatoide. Tamen, il es un facto generalmente recognoscite que neuropathia pote esser un characteristica de iste disordine. Nostre observationes non permitte un evalutation del possibilitate que le therapia a steroides adrenocortical jocava un rolo in le anormalitates del perception de vibrationes, como il es le caso in le vasculitis necrotisante que es incontrate occasionalmente in arthritis rheumatoide.

4. Le indice oscillometric esseva plus o minus normal in le patientes con gutta e in illes con arthritis rheumatoide.

SUMMARIO IN INTERLINGUA

(See page 301 for original article)

Le 17-Cetosteroides in Morbo Hepatic

Un basse excretion urinari de 17-cetosteroide esseva demonstrate in patientes con un variissime morbos hepatic. Iste constation es in harmonia con le hypothese: Un reducite catabolismo de precursores de 17-cetosteroide in consequentia del morbo hepatic → augmento de lor concentration efficace → inhibition del production e liberation de precursores de 17-cetosteroide → reducite excretion de metabolitos.

THE 17-KETOSTEROIDS IN LIVER DISEASE*

By Murray Franklin, M.D.†

William B. Bean, M.D.
PROFESSOR AND CHIEF OF MEDICINE

Harold Schedl, M.D., Ph.D.
RESEARCH ASSISTANT PROFESSOR OF MEDICINE

AND

James Embick, M.D.‡

(From the Department of Internal Medicine, State University of Iowa College of Medicine, Iowa City, Iowa)

The liver is the key organ in the metabolism of the steroid hormones: (a) C_{21} compounds of the pregnane series, such as the adrenal corticosteroids; (b) C_{19} compounds of the androstane series, such as the adrenal and testicular androgens; and (c) C_{18} compounds of the estrane series, such as the ovarian estrogens (Dorfman[3]). The C_{19} compounds are the main precursors of the urinary 17-ketosteroids, and the 24-hour urinary 17-ketosteroid excretion is an approximate integration of the total daily production of C_{19} compounds.§ This paper describes a study of the metabolism of these C_{19} compounds in normal subjects and in patients with liver disease by measuring urinary 17-ketosteroids.

Materials and Methods. Twenty-four hour urinary 17-ketosteroids of a group of 108 persons were analyzed by the method of Robbie and Gibson[6]. In over two-thirds of the cases urine specimens were collected for 2 successive days, both 24-hour specimens analyzed, and the results averaged. Several additional 24-hour urine specimens from many of the subjects were also analyzed. Tests of precision showed a variation of ± 5% for any stage of the method and an over-all variation of ± 10%. The groups studied consisted of 50 normal persons (33 men, 17 women) of different ages; 41 patients with portal cirrhosis (28 men, 13 women); 15 patients with acute hepatitis (9 men, 6 women) of different types (infectious, homologous serum, and toxic); and 2 men with congenital hemolytic jaundice. Many subjects considered normal had a variety of disorders such as benign prostatic hypertrophy, and convalescence from fractures or poliomyelitis. The diagnoses in the persons with liver disease were based upon clinical and laboratory studies which included needle or surgical biopsy in some, and necropsy in others. Extrahepatic obstructive jaundice was verified by operation. Of the many hepatic function tests used we are reporting data on total serum protein (Levinson and MacFate[4]), total serum cholesterol and cholesterol ester fraction (Schoenheimer and Sperry[7]), and alkaline phosphatase (Bodansky[2]) determinations. Urinary creatinine was analyzed to check the completeness of 24-hour urine collections.

*This work was supported in part by the Department of Medicine Trust Fund and grants from the Division of Research Grants and Fellowship of the National Institutes of Health, U.S. Public Health Service and the Commission on Liver Disease of the Armed Forces Epidemiological Board.

†Present address: 108 North State Street, Chicago 2, Illinois.
‡Present address: 180 Broadway, Richmond, California.

§A minor fraction of the 17-ketosteroids is derived from the hepatic degradation of C_{21} steroids of the pregnane series; for example, about 10 to 12% of a tracer dose of cortisol is excreted as 17-ketosteroids.

Results. NORMALS. Urinary 17-ketosteroids in 33 normal men ranged from 1.8 to 20.8 mg. per 24 hours, and averaged 9.7 mg. per 24 hours (Table 1, Fig. 1). The ages ranged from 18 to 80, values at the upper extreme of age (71 to 80 years) being responsible for a somewhat lower mean than in studies where extreme age groups are not included. When only the age groups from 21 to 60 years are considered, the mean is raised to 11.8 mg. per 24 hours (range 5.8 to 20.8 mg. per 24 hours). In normal women, the range was from 3.2 to 11.6 mg. per 24 hours with a mean of 6.5 mg. per 24 hours. When only the age groups from 21 to 60 years are considered, the mean for women rises to 7.7 mg. per 24 hours (range 5.3 to 11.6 mg. per 24 hours). These data agree with reported values.

HEPATITIS. The mean in 15 cases of acute hepatitis was 6.5 mg. per 24 hours (range 1.2 to 23.5 mg. per 24 hours). The wide range probably results from several factors: age, sex, severity and stage of disease as well as kind of disease. Figure 2 illustrates serial 17-ketosteroid determinations in the course of 2 cases of acute hepatitis: the levels are low in the acute stage and return to normal as the patient improves.

CIRRHOSIS. In the group of 41 patients with cirrhosis, the mean urinary 17-ketosteroid excretion was 4.2 mg. per 24 hours (range 0.7 to 9.2 mg. per 24 hours, Table 1, Fig. 1). The mean for the men was 4.8 mg. per 24 hours (range 1.1 to 9.2 mg. per 24 hours). The mean for the women was 2.9 mg. per 24 hours (range 0.7 to 9.2 mg. per 24 hours). Figure 1 shows that while most of the patients with cirrhosis had very low urinary excretions of 17-ketosteroids, there were several with normal levels. Unlike the situation with acute hepatitis where corre-

TABLE 1.—24-HOUR URINARY 17-KETOSTEROID EXCRETION WITH RESPECT TO AGE IN NORMAL SUBJECTS AND PATIENTS WITH LIVER DISEASE

AGE GROUPS		NORMALS			HEPATITIS										CIRRHOSIS			OBSTRUCTIVE JAUNDICE							HEMOLYTIC JAUNDICE	
					Inf.		HSJ		Tox Hep		Total							Benign			Malignant					
		M	F	TOTAL	M	F	M	F	M	F	M	F	TOTAL M & F		M	F	TOTAL M & F	M	F	TOTAL	M	F	TOTAL	TOTAL B & M	M	F
10 - 20	No. Cases	2	2	4											2	2	4								-	
	Mean Value	6.1	5.0	5.6	-	-	-	-	-	-	-	-	-		4.5	4.7	4.6	-	-	-	-	-	-	-	2.4	-
	Range MG/24HRS	5.3 6.8	4.0 6.0	4.0 6.8											3.9 5.0	4.2 5.5	3.9 5.5								2.2 2.5	
21 - 40	No. Cases	10	6	16	5	4	1	1		1	6	6	12		6	5	11				1	1	2	2		
	Mean Value	11.9	7.9	10.4	8.6	4.8	3.7	2.3	-	6.6	7.8	4.5	6.2		6.0	2.9	5.4	-	-	-	4.2	2.3	3.3	3.3	-	-
	Range MG/24HRS	5.8 18.8	5.3 11.6	5.8 18.8	1.7 23.5	1.2 6.5					1.2 23.5	1.2 6.5	1.2 23.5		1.1 9.1	1.5 4.9	1.1 9.1						2.3 4.2	2.3 4.2		
41 - 60	No. Cases	11	3	14	1	-			1		2		2		14	6	20	1	1	2	1	3	4	6		
	Mean Value	11.7	7.2	10.7	12.0	-	-	-	7.6	-	9.8	-	9.8		4.4	2.3	3.7	3.9	3.3	3.6	3.9	2.4	2.8	3.1	-	-
	Range MG/24HRS	5.7 20.8	5.9 9.4	5.7 20.8							7.6 12.0		7.6 12.0		1.2 9.2	0.7 4.7	0.7 9.2			3.3 3.9			2.6 3.9	2.4 3.9		
61 - 70	No. Cases	3	4	7											5		5				4		4	4		
	Mean Value	9.8	5.9	7.6	-	-	-	-	-	-	-	-	-		4.0	-	4.0	-	-	-	4.2	-	4.2	4.2	-	-
	Range MG/24HRS	5.7 12.6	3.2 9.0	3.2 12.6											1.4 7.9		1.4 7.9				1.7 10.1		1.7 10.1	1.7 10.1		
71 - 80	No. Cases	7	2	9					1		1		1		1		1				2	2	4	5		
	Mean Value	4.4	4.1	4.3	-	-	-	-	1.3	-	1.3	-	1.3		4.6	-	4.6	-	0.8	0.8	3.5	2.3	2.7	2.3	-	-
	Range MG/24HRS	1.8 9.8	3.6 4.6	1.8 9.8																	2.4 4.6	1.8 2.8	1.8 4.6	1.8 4.6		
TOTALS	No. Cases	33	17	50	6	4	1	1	2	1	9	6	15		28	13	41	1	2	3	8	6	14	17	2	
	Mean Value	9.7	6.5	8.6	9.0	4.5	3.7	2.3	4.4	6.6	7.8	4.5	6.5		4.8	2.9	4.2	3.9	2.1	2.7	4.0	2.4	3.3	3.2	2.4	-
	Range MG/24HRS	1.8 20.8	3.2 11.6	1.8 20.8	1.7 23.5	1.2 6.5			1.3 7.6		1.2 23.5	1.2 6.5	1.2 23.5		1.1 9.2	0.7 5.5	0.7 9.2		0.8 3.3	0.8 3.9	1.7 10.1	1.8 2.8	1.7 10.1	0.8 10.1	2.2 2.5	

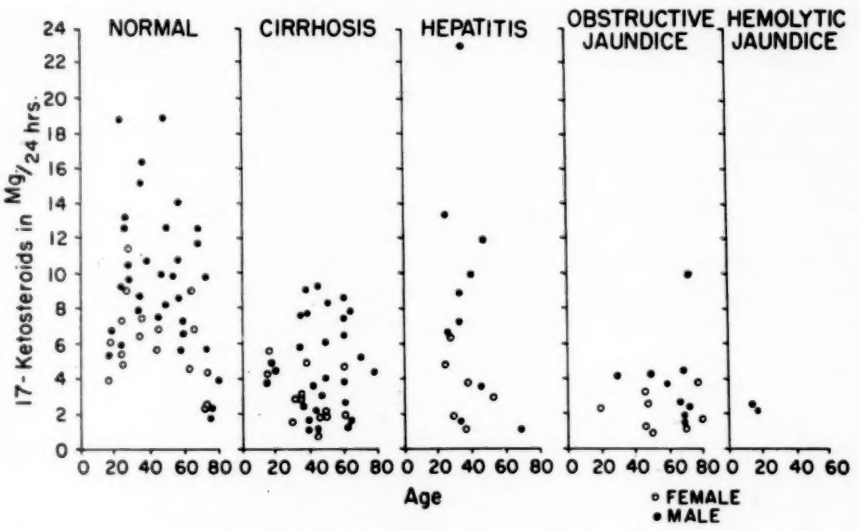

Fig. 1.—24-hour urinary 17-ketosteroid excretion with respect to age in normal subjects and patients with liver disease.

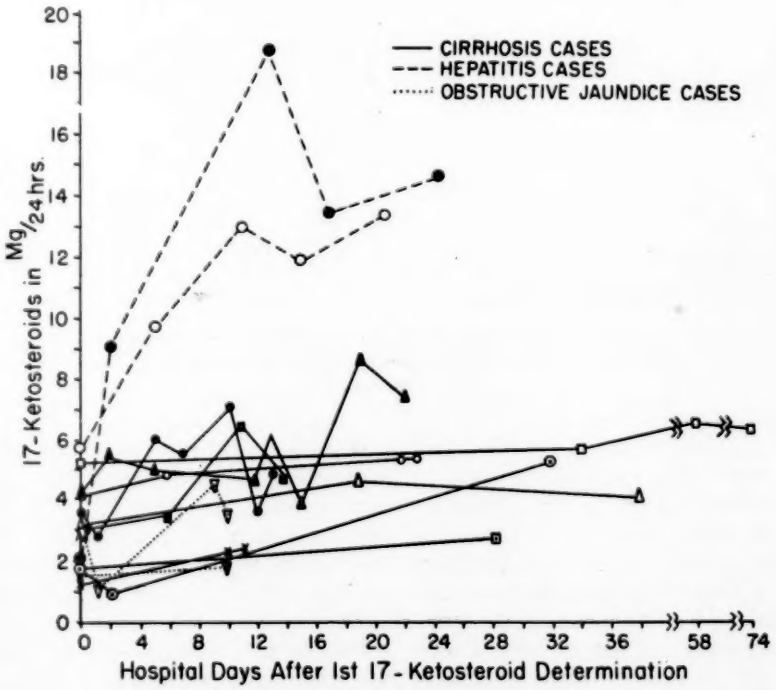

Fig. 2.—Pattern of serial 17-ketosteroid analyses in patients with liver disease. Note persistently low values in cirrhosis and obstructive jaundice in contrast to the regaining of normal levels in patients with infectious hepatitis as clinical improvement occurs.

lation between stage of disease and 17-ketosteroid excretion was good, in the cirrhotic 17-ketosteroid excretion tended to be low regardless of the stage of the disease.

In cirrhosis, unlike acute hepatitis, significant elevation of 17-ketosteroid excretion did not occur when serial determinations were made over periods of days to months (Fig. 2). However, unlike the patients with acute hepatitis, most of the patients with cirrhosis (range 1.7 to 10.1 mg. per 24 hours). The low excretion was not related to the age of the subjects. Women consistently excreted less than men.

HEMOLYTIC JAUNDICE (Table 1, Fig. 1). Both patients were young men in the 10- to 20-year age group and had congenital hemolytic jaundice. They were retarded in growth and sexual development, which undoubtedly contributed to the low levels found in these 2 patients.

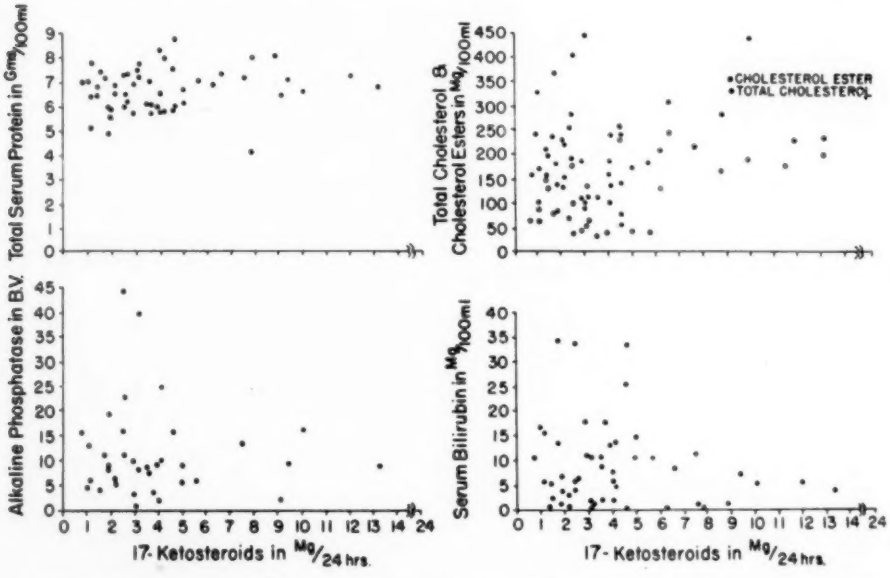
Total Serum Protein in Gms/100ml
Total Cholesterol & Cholesterol Esters in Mg/100ml
•CHOLESTEROL ESTER
•TOTAL CHOLESTEROL
Alkaline Phosphatase in B.V.
Serum Bilirubin in Mg/100ml
17- Ketosteroids in Mg/24 hrs.
17- Ketosteroids in Mg/24 hrs.

Fig. 3.—24-hour urinary 17-ketosteroid excretion and liver function tests. Note slight correlation with cholesterol esters. A high serum bilirubin is associated with low urinary 17-ketosteroids.

did not improve. They reached a low plateau which they did not exceed.

OBSTRUCTIVE JAUNDICE. The 17-ketosteroid excretion was low in patients with extrahepatic obstructive jaundice (Table 1, Fig. 1) of both benign and malignant types. The mean for patients with obstruction of benign origin was 2.7 mg. per 24 hours (range 0.9 to 3.9 mg. per 24 hours). The mean for patients with obstruction caused by malignancy was 3.3 mg. per 24 hours

Correlation between 17-ketosteroid excretion and the standard hepatic function tests was poor (Fig. 3). There is a suggestion of a correlation between cholesterol esters and 17-ketosteroid excretion. Patients with high serum bilirubin invariably showed low 17-ketosteroid excretion; the converse was not true, since patients with low serum bilirubin had low as well as normal levels of 17-ketosteroid excretion. 17-Ketosteroid excretion correlates fairly

well with creatinine excretion, and less well with urine volume (Fig. 4).

Discussion. The finding that urinary excretion of 17-ketosteroids is low in patients with liver disease agrees with the experience of other workers (Birke and Plantin[1], Peterson, Guerra and Sborov[5]). A variety of explanations has been advanced for this finding. We believe it to be the result of the liver disease. At the onset of liver damage the decreased rate of metabolism of 17-ketosteroid precursors must result in an initial rise in the concentration of these substances in the blood. The increased concentration of 17-ketosteroid precursors would then suppress their production or release, or both, via homeostatic control mechanisms. Because of the decreased requirement resulting from decreased hepatic destruction, a new equilibrium based on decreased production rate would result. The decreased daily production of 17-ketosteroid precursors would then result in a lowered 24-hour 17-ketosteroid excre-

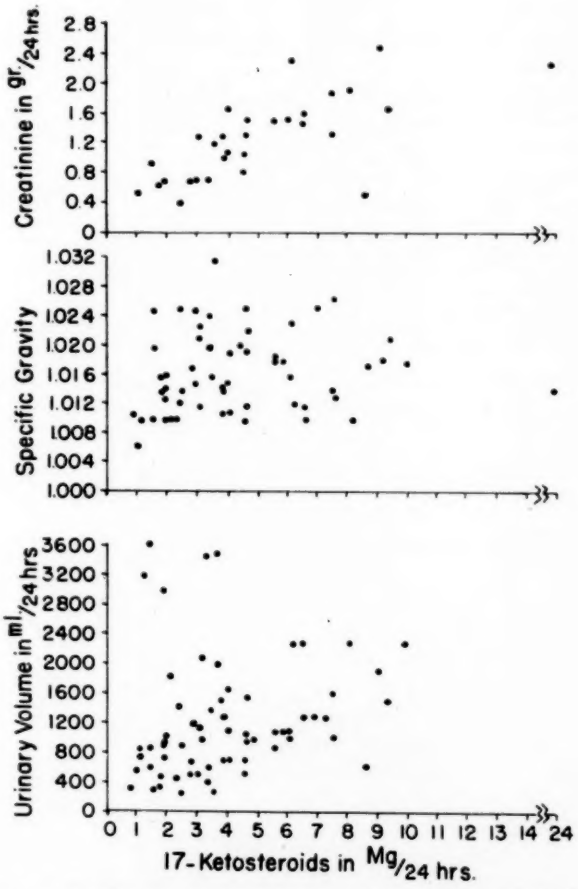

Fig. 4.—Comparison of 24-hour urinary 17-ketosteroid excretion with the volume, specific gravity, and creatinine content of the specimens. The best correlation is with creatinine.

tion, since the latter is a rough integration of daily production. Thus, in chronic liver disease, a relatively stable equilibrium of decreased catabolism coupled with decreased production results in chronically low 17-ketosteroid excretion.

The pattern of the serial 17-ketosteroid determinations in acute hepatitis fits this concept. The initial low levels are followed by a rise to normal values as liver function improves. Metabolism of 17-ketosteroid precursors undergoes acute impairment initially at the time of maximum insult to the liver. This would result in an initial rise in blood level and consequent fall in adrenal production or release of 17-ketosteroid precursors, or both. With the return of liver function to normal, the increased metabolism would lead to increased production of 17-ketosteroid precursors required to maintain equilibrium and is reflected by the return of 17-ketosteroid excretion to normal values.

The reason for the hormonal imbalance associated with liver disease is difficult to understand. We assume that at the time impairment of hepatic function begins there is initially an excess of all hormones metabolized by the liver. Thereafter, homeostatic mechanisms reach a new equilibrium where hormonal balance is re-established. Thus, even with a differential impairment of the liver's ability to metabolize C_{21} corticosteroids and C_{19} steroids from the adrenal and testis as compared with C_{18} estrane derivatives, it is difficult to account for the hormonal imbalance. If adrenal estrogen production were to continue unabated despite a decreased rate of hepatic inactivation, the relative excess of estrogen would cause hormonal imbalance.

The testicular atrophy associated with liver disease might be explained as follows: since there is a dual source for the androgenic 17-ketosteroid precursors, that is, both adrenal and testis, an increase in adrenal androgens might depress pituitary factors controlling the testis. Thus, testicular atrophy might result in the presence of circulating adrenal androgen, by the same mechanism that androgen administration produces testicular atrophy.

Summary. Low urinary 17-ketosteroid excretion has been demonstrated in patients with a wide variety of liver diseases. This finding is consistent with the hypothesis: decreased catabolism of 17-ketosteroid precursors because of liver disease → rise in their effective concentration → inhibition of production and release of 17-ketosteroid precursors → decreased excretion of metabolites.

REFERENCES

1. **Birke, G.**, and **Plantin, L. O.**: Acta med. Scandinav., Supplement 291, **148**, 1954.
2. **Bodansky, A.**: Am. J. Clin. Path. (Tech. Supp.), **1**, 51, 1937.
3. **Dorfman, R. I.**: *in* **Pincus, G.**, and **Thiman, K. V.**: The Hormones, Vol. III, Chapter 12, New York: Academic Press, Inc., 1955.
4. **Levinson, S. A.**, and **MacFate, R. P.**: Clinical Laboratory Diagnosis, 4th ed. Philadelphia: Lea & Febiger, 1951.
5. **Peterson, R. E., Guerra, S.**, and **Sborov, V. M.**: J. Lab. & Clin. Med., **43**, 58, 1954.
6. **Robbie, W. A.**, and **Gibson, R. B.**: J. Clin. Endocrinol., **3**, 200, 1943.
7. **Schoenheimer, R.**, and **Sperry, W. M.**: J. Biol. Chem., **106**, 745, 1934.

(Interlingua on page 300)

RESPIRATORY AND CARDIAC DEATHS IN LOS ANGELES SMOGS DURING 1956, 1957 AND 1958

By C. A. Mills, M.D.
PROFESSOR OF EXPERIMENTAL MEDICINE, UNIVERSITY OF CINCINNATI
CINCINNATI, OHIO

Ozone smogs continue to keep pace with the ever-increasing numbers of liquid-fuel motors operating in today's urban areas. It thus remains important that associated community health hazards be kept closely evaluated. The Los Angeles metropolitan area still remains the best locality for such evaluation, with the most complete and continuous air pollution data anywhere available.

Our earlier studies, showing a significant relationship between respiratory-cardiac deaths and Los Angeles smogs, have been criticized as not being based on actual smog analysis[5], or on the relating of oxidant readings from Pasadena alone to deaths throughout the whole county[6], or because of my attempts at daily death adjustments to eliminate seasonal trends and secure comparable death data throughout the year for correlation studies. In the present study on data for the years, 1956, 1957 and 1958, all these points of criticism have been eliminated, but without changing in any way the earlier findings on positive death-smog relationships.

In Table I are presented three sets of data for the 3 years (1956, 1957 and 1958): 1) daily death data for Los Angeles County from respiratory and cardiac causes (ISC #470-527, 400-468) kindly supplied by the California Department of Public Health; 2) the daily average of the highest measured oxidant concentrations (potassium iodide method) recorded at all of the several stations operated by the Los Angeles County Air Pollution Control District; and 3) the Los Angeles daily maximum temperatures as obtained from Weather Bureau records.

The data for 1955 were not included in the analysis since daily oxidant maxima were available for only one station during the first 6 months and coverage was too incomplete to be of value for the additional stations established during the latter half of the year. Oxidant data kindly supplied by the L.A. County Air Pollution Control District included daily maximum readings at the following numbered station locations:

1. 434 S. San Pedro St., Los Angeles
2. 4409 W. Pico Blvd., W. Los Angeles
3. 6122 ½ N. Figueroa St., Highland Park
4. Raymond Ave. & Holly St., Memorial Park, Pasadena; Colorado & Fair Oaks, Pasadena
5. 8841 E. Slawson Ave., Rivera
6. 2720 ½ Peck Rd., El Monte
7. 827 N. Azusa Ave., Azusa
8. 19947 E. Valley Blvd., Walnut
9. 1508 Burbank Blvd., Burbank
11. 19630 Sherman Way, Pasadena
12. 4436 West Imperial Highway, Lennox
13. 1657 Gramercy Ave., Torrence
15. 5201 Santa Fe Ave., Vernon
58. Fifth and Olive Sts., Pershing Sq., Los Angeles
59. 301 Coast Blvd., El Segundo, Los Angeles
60. 803 Loren Ave., Azusa
61. 844 S. LaBrea, W. Los Angeles
62. 21505 S. Avalon, Dominguez

TABLE 1.—DAILY RESPIRATORY AND CARDIAC DEATHS(D), AVERAGE OF

	Jan.			*Feb.*			*March*			*April*			*May*			*June*		
Day	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*
1	66	11	71	75	6	76	74	7	67	70	5	61	61	8	69	64	15	76
2	69	11	64	61	5	66	61	6	67	80	6	63	63	7	68	59	16	77
3	77	12	70	70	3	62	75	12	65	76	5	63	69	13	73	58	16	77
4	84	11	73	79	5	63	70	9	73	66	6	62	60	21	84	60	0	79
5	60	9	77	72	8	64	58	15	72	65	8	65	71	23	79	54	12	77
6	64	9	72	63	12	68	62	4	54	68	4	57	64	13	77	55	16	77
7	85	13	79	56	14	66	60	6	60	75	7	62	53	9	69	51	10	78
8	73	19	74	75	7	63	76	9	64	77	15	72	69	11	69	58	9	77
9	66	23	70	75	9	67	67	8	66	87	22	75	75	7	67	65	13	80
10	77	14	64	92	14	67	62	6	66	78	24	83	59	8	69	65	13	76
11	65	16	66	81	17	70	61	9	59	71	17	87	62	6	67	55	9	74
12	69	14	67	73	8	62	82	6	60	62	14	86	62	10	73	47	8	76
13	64	12	64	84	8	69	71	4	59	68	20	83	60	17	75	61	15	77
14	95	13	70	76	15	68	80	4	61	84	15	88	59	25	83	62	30	86
15	70	17	75	71	20	70	86	3	56	78	16	91	69	28	84	56	20	82
16	88	22	80	67	27	78	78	6	69	69	9	76	56	20	77	57	23	84
17	76	17	80	81	29	77	82	4	65	74	17	75	68	19	79	47	17	81
18	84	13	73	71	8	63	59	11	67	74	14	72	67	18	79	68	15	84
19	93	8	70	62	4	64	80	19	73	66	23	86	70	19	81	71	14	83
20	87	10	69	57	18	72	74	4	62	69	23	96	60	21	82	71	15	84
21	71	9	63	77	21	76	73	4	65	79	26	91	70	21	70	71	16	83
22	68	13	66	51	8	66	88	6	66	63	14	79	58	20	80	59	15	86
23	74	11	67	70	11	66	83	4	64	68	15	77	60	15	82	44	17	87
24	88	2	57	71	9	66	73	7	66	70	11	75	56	17	81	63	13	82
25	79	5	64	68	4	67	90	11	68	67	16	73	53	16	81	62	13	84
26	66	4	64	74	6	68	77	11	68	68	18	73	74	21	83	57	18	84
27	74	15	68	77	12	69	79	4	60	61	17	75	57	16	81	53	19	85
28	64	17	70	75	11	66	67	7	62	68	13	72	71	26	87	50	23	85
29	65	8	62	—	—	—	61	9	66	69	9	69	70	26	85	53	13	81
30	76	11	65	—	—	—	73	7	64	71	8	67	50	9	80	47	16	81
31	63	7	72	—	—	—	83	5	64		–		63	15	78	—	—	—
Aver.	74.8	12.1	69.2	71.5	11.4	67.8	73.1	7.3	64.5	71.4	13.9	75.1	63.2	16.3	77.4	58.1	15.3	80.8

63. San Vicente & Wilshire Blvd., Sawtelle
64. 862 Villa St., Pasadena

For the year 1956, data supplied covered stations 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 15, 56, and 58; for 1957, additional stations 59, 60, and 61; and for 1958, 1, 4, 5, 8, 9, 12, 13, 15, 58, 59, 60, 61, 62, 63, and 64. The data series were not complete for all days at every station, but the coverage afforded seemed adequate to provide a fairly stable average daily maximum figure.

Since respiratory and cardiac deaths rise sharply during the heat waves of Los Angeles' worst smog months, the suggestion has been put forth repeatedly that it is the heat, not the oxidant smogs, which bring on the rise in such deaths. Certainly no one doubts that excessive heat can kill, but most studies (Borden, Waddill and Grier[2], Ferris *et al.*[3], Harrison[4], Mills[7] and Mills and Ogle[8]) have found heat deaths largely restricted to temperatures above 95°

OXIDANT MAXIMA(O), AND TEMPERATURE MAXIMA(T), FOR YEAR 1958.

	July			*August*			*September*			*October*			*November*			*December*		
Day	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*
1	41	12	81	57	14	86	54	15	84	60	26	87	74	20	80	82	15	77
2	63	13	81	46	15	85	55	15	82	40	24	99	77	19	82	59	23	85
3	61	14	81	66	15	86	48	14	81	68	16	102	73	21	83	90	24	89
4	58	14	80	56	21	84	55	19	83	57	22	99	57	29	83	85	17	75
5	67	15	82	47	15	84	59	23	91	57	10	81	63	32	78	66	10	66
6	78	12	79	70	14	85	59	16	93	53	7	76	81	35	82	76	18	67
7	59	19	84	74	14	84	71	15	92	59	13	76	51	22	73	61	19	66
8	59	22	90	71	16	82	68	19	90	61	18	77	66	25	75	64	16	63
9	59	32	93	58	20	89	53	23	90	67	19	77	56	17	70	64	26	66
10	60	30	95	53	21	89	57	18	88	68	18	77	58	6	67	85	24	86
11	67	30	88	38	14	87	71	21	84	43	17	77	61	6	65	74	21	85
12	60	21	88	58	20	90	51	13	82	49	21	81	69	7	68	75	19	79
13	60	15	83	54	17	87	54	13	78	58	29	91	50	18	71	74	24	76
14	49	15	80	61	20	92	54	16	86	50	36	94	65	14	68	80	9	83
15	66	13	79	73	15	84	77	25	96	71	27	101	68	6	60	80	4	77
16	56	15	79	74	17	86	52	25	96	76	23	104	71	7	57	62	14	82
17	53	16	80	49	12	82	61	23	90	71	27	102	75	12	61	75	14	81
18	57	19	81	57	13	81	57	30	92	65	40	91	83	15	68	74	19	73
19	52	16	81	55	13	82	68	33	89	46	14	82	68	17	60	80	14	65
20	65	13	81	49	14	81	53	29	92	65	13	80	78	17	57	78	27	72
21	51	18	81	51	14	81	41	20	84	60	15	83	80	19	80	83	19	67
22	49	14	79	64	15	81	47	10	77	46	17	77	74	33	80	94	18	64
23	65	14	79	45	14	80	58	3	67	52	7	71	82	36	77	64	10	66
24	48	12	81	58	14	83	56	14	81	53	8	71	73	22	72	54	11	66
25	55	15	80	64	16	86	49	23	90	65	5	68	78	18	73	67	10	65
26	51	15	82	66	13	86	77	32	94	48	14	71	71	11	70	71	12	65
27	62	13	82	49	14	83	67	20	92	66	17	74	77	15	68	94	6	61
28	69	19	82	61	17	83	63	19	91	58	30	80	74	17	76	58	9	66
29	58	16	80	52	16	81	64	22	85	62	21	88	72	10	75	72	11	71
30	48	25	94	62	18	84	54	21	84	52	14	84	61	12	76	77	8	70
31	56	19	89	44	17	83				65	11	80				57	9	75
Aver.	58.3	17.3	83.1	57.5	15.8	84.4	58.4	19.6	86.9	58.4	18.7	83.9	69.5	17.9	73.2	73.3	15.2	72.5

F. unless there is an associated high humidity. In our study of oxidant-death relationships in the low-humidity heat of Los Angeles, therefore, we have excluded from these calculations all days with drybulb temperatures in excess of 96° F.

The first important finding in our analysis of the data in Table 1 is that oxidant maxima are clearly and significantly related to daily temperature maxima at all seasons of the year and at daily temperature maxima ranging from 46° F. to 104° F.

This evident relationship between oxidant and temperature maxima is of a high degree of mathematical significance, as indicated by the correlation coefficients calculated for the January-February and July-August periods of each of the 3 years:

	January-February	*August-July*
1956–	r = .676, p>.0001	r = .628, p>.0001
1957–	r = .539, p>.0001	r = .438, p>.001
1958–	r = .726, p>.000.	r = .635, p>.0001

The second finding of great importance is that a clear relationship exists

TABLE 1. (continued) YEAR 1957

	January			*February*			*March*			*April*			*May*			*June*		
Day	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*
1	81	9	68	77	14	64	66	6	64	63	6	68	52	14	72	58	20	81
2	73	13	74	100	9	59	59	6	63	67	9	79	53	12	71	72	20	89
3	89	11	68	59	8	64	56	9	66	70	13	76	63	19	76	73	31	94
4	89	2	57	64	13	68	66	13	70	65	14	76	61	16	78	57	20	94
5	82	4	62	84	12	72	66	7	67	54	19	74	67	10	71	58	20	83
6	59	5	67	88	15	72	69	16	75	64	7	61	44	11	73	64	14	80
7	71	4	57	72	13	63	60	26	84	52	8	72	48	6	67	66	11	73
8	65	5	63	77	6	63	59	10	65	62	19	78	67	3	70	65	5	70
9	89	6	66	52	7	68	69	3	59	70	10	70	63	7	69	52	5	71
10	64	3	59	88	14	76	56	11	71	61	11	66	50	5	68	50	7	72
11	74	4	63	72	14	78	46	8	68	62	9	64	55	3	62	63	12	75
12	63	2	63	78	18	88	63	7	66	73	11	68	60	5	68	54	18	78
13	60	3	63	62	26	86	62	7	69	66	19	72	44	6	69	47	8	68
14	72	8	62	69	16	79	71	18	74	65	9	71	56	5	69	70	10	73
15	65	10	64	64	5	60	70	13	70	63	8	73	48	11	73	49	9	74
16	59	12	73	70	3	60	54	4	62	54	5	65	54	16	77	62	18	87
17	64	12	72	62	26	60	55	4	57	64	7	64	72	12	76	81	11	100
18	51	10	72	72	16	63	68	6	65	62	5	66	59	6	68	76	19	104
19	64	12	67	76	5	60	51	11	74	54	6	63	57	4	71	88	23	96
20	67	4	54	70	3	63	57	10	74	51	4	57	63	6	67	66	17	86
21	79	9	60	57	12	65	60	5	64	76	7	63	66	8	71	57	13	86
22	62	11	61	62	11	68	71	6	69	53	4	59	78	6	72	66	13	80
23	58	3	51	56	4	68	59	9	73	76	7	63	56	7	68	71	17	85
24	77	2	56	65	7	67	69	15	77	67	10	68	67	10	72	47	27	85
25	69	4	61	75	13	69	75	22	77	61	14	70	56	22	79	58	18	87
26	79	4	53	66	15	68	70	20	75	47	25	79	51	18	83	57	20	85
27	51	4	48	70	15	69	77	20	85	67	24	79	65	10	77	59	11	83
28	74	5	49	63	6	62	74	22	82	52	17	85	65	8	71	57	9	79
29	68	4	49				61	10	76	59	18	75	61	8	70	38	9	80
30	80	6	58				73	10	72	65	13	72	53	11	71	57	9	78
31	82	10	61				72	12	73				61	18	79			
Aver.	70.7	6.8	61.3	70.4	10.5	67.9	64.0	11.2	70.5	62.2	11.3	69.9	58.6	9.8	71.9	61.3	14.8	75.9

between excess respiratory and cardiac deaths and prevailing average oxidant maxima over the 3-year period. In order to establish this finding the oxidant maxima (average for all stations) for each day was related to that day's deviation from the month's daily average for such deaths. Table 3 presents the 3-year summation of such daily deviation from the monthly average, grouped by increasing oxidant concentrations.

In Table 3 there is an evident gradation upward in the number of excess respiratory and cardiac deaths (above the daily average for each month), rising from a deficit of —2.03 per day at the 0 to 4 pphm oxidant levels as the zero grouping, the days with oxidant maxima of 35 pphm or over exhibit an excess of 5.03 respiratory and cardiac deaths per day. The total excess above the zero grouping would be 881 deaths for the 3-year period. Since

TABLE 1. (Continued) YEAR 1957

	July			*August*			*September*			*October*			*November*			*December*		
Day	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*
1	72	16	84	60	19	95	62	19	84	73	18	82	68	7	72	83	11	77
2	54	20	92	63	15	90	76	11	81	62	15	76	56	4	66	84	21	77
3	61	24	96	44	15	85	56	16	80	51	6	74	61	4	62	63	9	81
4	50	20	102	64	16	83	49	17	82	58	14	75	70	7	66	79	8	72
5	67	9	90	44	15	82	58	20	84	43	22	77	65	8	64	67	5	57
6	55	10	87	61	11	82	50	23	88	65	12	75	76	11	67	82	12	66
7	52	15	87	48	15	80	57	23	89	59	21	76	69	14	69	73	18	74
8	56	16	93	59	15	83	54	15	88	79	25	80	83	23	70	74	19	80
9	62	13	85	63	15	85	55	17	83	59	22	82	85	26	72	87	16	84
10	50	14	81	51	15	85	44	18	80	65	15	75	70	21	70	72	22	82
11	57	17	91	55	17	84	58	22	81	70	4	71	79	17	69	64	18	82
12	51	14	88	58	23	87	52	18	81	49	7	69	75	15	72	67	16	78
13	46	15	85	55	15	90	66	12	81	52	6	67	72	11	67	81	10	73
14	57	22	89	53	19	91	57	11	78	67	10	72	65	8	65	81	5	68
15	62	22	93	65	20	90	52	18	80	69	5	70	80	8	66	72	2	64
16	59	18	88	61	22	94	57	12	74	57	18	75	68	7	63	83	3	66
17	39	8	80	60	19	93	73	8	76	72	25	80	79	9	66	79	9	66
18	55	12	82	55	12	90	53	15	79	53	6	68	80	14	69	65	6	60
19	57	14	83	57	14	91	52	16	78	60	9	69	77	13	69	76	11	66
20	51	14	83	56	16	89	58	15	77	57	4	67	85	24	81	69	17	71
21	49	10	80	54	13	84	50	29	81	80	9	69	64	9	78	61	15	66
22	59	14	83	58	20	92	63	30	88	72	9	70	86	5	68	84	8	63
23	72	15	84	51	21	90	57	30	85	80	15	74	73	14	74	70	12	69
24	54	20	86	57	16	88	62	37	90	58	21	81	74	22	79	69	16	68
25	49	15	83	42	16	90	59	16	85	71	26	88	90	27	83	87	15	76
26	60	12	81	48	21	86	57	17	80	88	14	81	70	22	72	72	15	73
27	47	14	82	45	30	92	58	26	84	72	11	86	85	21	70	83	12	68
28	56	11	81	48	23	87	60	30	87	68	10	75	75	17	72	67	13	68
29	69	18	87	59	7	78	53	19	87	63	14	81	91	12	76	69	20	71
30	53	22	94	54	13	77	57	20	85	59	7	77	65	5	76	77	12	73
31	73	25	94	52	14	82				73	6	70				73	11	76
Aver.	56.6	15.8	86.9	54.2	16.8	86.9	57.2	19.5	82.5	65.0	13.1	75.2	74.5	13.5	70.4	74.6	12.5	71.5
	(56.8 30 days)																	

this first calculation is based upon monthly means which themselves are obviously influenced by prevailing oxidant levels, we have made a separate grouping for the 5-month period of January through May (second section of Table 3) and then used this as a basis for calculation of upward corrections in daily deaths for the months of higher oxidant readings. Such correction indicates that 240 more deaths should be added to the 881 indicated in the first section of Table 3, giving a grand total of 1121 excess respiratory and cardiac deaths associated with oxidant maxima above the 0 to 4 pphm base level during the 3-year period. It can scarcely be a coincidence that this represents only a slightly higher excess than the 334 for 1954 reported in our previous study[6].

The use of correlation methods to the oxidant-death data of Table 1 yields significant findings only during those

TABLE 1. (Continued) YEAR 1956

	January			*February*			*March*			*April*			*May*			*June*		
Day	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*
1	65	11	61	56	12	64	74	21	68	69	5	60	66	10	67	48	26	82
2	76	15	67	66	10	62	66	17	74	64	11	63	51	21	68	54	20	76
3	83	14	77	59	15	64	78	15	69	82	10	63	53	15	70	63	17	78
4	66	22	71	71	20	65	69	13	65	70	13	73	48	4	67	64	14	76
5	75	20	65	65	8	57	79	8	62	56	11	71	63	5	70	57	12	75
6	67	20	65	74	10	65	71	6	63	55	21	71	63	5	68	60	14	75
7	66	22	65	58	14	65	70	14	67	62	14	70	68	9	70	58	20	77
8	94	17	66	59	9	65	73	19	76	78	10	67	62	10	71	46	26	78
9	61	26	66	55	10	68	66	22	74	63	13	69	61	4	66	49	23	78
10	63	15	63	81	18	70	60	14	70	75	4	60	55	8	67	65	21	80
11	70	19	73	64	32	70	81	9	60	64	4	60	56	10	66	62	25	89
12	80	29	75	77	18	59	67	8	66	57	3	51	59	12	69	57	26	90
13	77	16	68	64	7	56	71	12	67	68	4	55	78	15	80	71	25	89
14	70	3	56	79	9	60	78	9	65	77	9	63	58	13	85	42	12	78
15	68	5	59	66	7	59	68	18	75	73	10	64	69	18	96	48	12	78
16	75	7	68	74	6	57	73	13	82	68	9	63	78	20	99	50	18	76
17	56	12	67	68	9	58	69	24	83	56	7	62	69	15	82	59	16	77
18	79	20	70	67	8	58	65	21	74	55	5	61	48	21	82	45	12	73
19	70	15	64	62	10	58	72	17	67	69	21	74	53	18	79	48	13	77
20	59	4	55	65	11	63	66	17	71	85	18	86	48	12	77	52	14	73
21	52	12	64	68	13	67	69	17	78	59	24	78	59	16	78	40	14	77
22	46	4	58	68	6	60	73	12	66	63	22	78	55	19	73	48	16	78
23	45	4	60	70	3	54	82	25	76	69	12	65	57	16	68	49	18	79
24	66	6	61	82	7	58	77	22	77	63	9	69	43	6	64	61	18	80
25	60	2	54	78	9	59	73	15	68	68	7	67	58	5	64	48	22	81
26	60	2	56	73	9	62	65	11	67	48	5	63	56	7	66	55	22	87
27	84	5	62	80	12	65	75	12	76	68	5	65	56	8	65	55	22	88
28	54	10	59	74	18	66	77	14	84	79	12	67	63	10	67	53	16	88
29	70	7	59	66	12	64	58	16	79	49	10	69	49	10	66	57	11	85
30	64	6	60				58	13	71	62	12	65	51	11	70	54	8	80
31	69	7	61				52	5	60				52	17	74			
Aver.	67.4	12.3	63.7	67.9	11.5	62.0	70.2	14.8	71.0	65.7	10.9	66.5	58.2	11.9	72.7	53.9	17.4	79.8

months when daily oxidant figures are fairly evenly balanced above and below 15 pphm in number of days. Thus, September of 1948 had 11 of its 30 days at oxidant levels below 15 pphm and exhibited a correlation coefficient of $r = .440$, $.02<p>.01$, while the Septembers of 1956 and 1957 had only 3 and 5 days with oxidant below 15 pphm and exhibited insignificant correlation coefficients. Wide day-to-day fluctuations in these deaths provide the main handicap to direct correlation studies, overshadowing the lesser variations associated with oxidant level as only one of the many potential causes of such deaths. It is thus doubly significant that associations of such positive character as those carried out in Table 3 should emerge.

Discussion. From this analysis of 1956, 1957, and 1958 data, it becomes obvious 1) that Los Angeles oxidant maxima are directly and significantly related to temperature maxima at ranges from 46° to 104° F., and 2)

TABLE 1. (Continued) YEAR 1956

	July			*August*			*September*			*October*			*November*			*December*		
Day	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*	*D*	*O*	*T*
1	49	5	75	54	13	80	41	19	82	57	13	80	56	5	70	68	19	77
2	45	7	72	43	12	76	60	19	81	63	6	78	69	10	72	67	22	75
3	55	11	73	48	12	76	49	17	81	57	13	80	80	8	72	75	18	64
4	69	15	78	53	15	79	51	20	85	58	3	69	75	9	72	60	11	64
5	55	21	79	43	20	84	41	16	82	48	10	76	69	20	76	72	6	61
6	54	21	81	61	19	83	62	20	84	65	11	73	65	18	91	85	6	61
7	63	17	82	64	16	83	59	26	87	67	9	76	87	15	91	61	5	61
8	43	14	79	51	20	83	63	33	90	51	16	79	72	12	93	69	9	64
9	59	26	84	69	23	84	54	26	102	73	27	80	84	11	94	77	12	74
10	46	20	85	53	23	82	73	29	101	49	22	79	78	14	93	73	12	70
11	66	23	81	58	15	79	56	18	89	58	9	73	70	15	86	64	13	68
12	55	10	77	41	15	79	57	19	83	57	12	74	78	23	78	73	19	73
13	49	13	80	58	18	80	64	25	85	55	14	76	61	12	64	73	17	77
14	41	14	79	53	17	82	60	25	90	55	14	75	67	13	72	67	15	72
15	67	10	81	46	21	85	50	25	93	61	17	78	68	9	76	79	19	73
16	70	17	83	46	14	84	66	14	93	52	17	74	57	8	80	77	13	73
17	61	18	82	49	12	81	57	24	93	56	17	74	62	12	83	72	18	78
18	62	17	85	46	17	81	65	24	90	52	12	68	60	12	77	64	11	75
19	46	19	82	59	15	79	51	20	89	60	22	78	68	8	69	66	10	76
20	40	15	84	55	23	82	54	14	81	72	19	89	70	5	67	62	4	75
21	63	15	83	52	26	86	46	26	85	56	15	85	56	11	80	79	10	64
22	61	15	87	68	25	94	58	17	83	66	12	76	57	10	82	59	9	66
23	54	21	87	64	24	98	52	17	86	55	4	69	83	18	82	74	10	70
24	56	15	82	70	16	91	53	26	91	45	9	71	67	12	85	74	13	78
25	51	18	85	55	16	85	50	32	91	68	10	79	70	9	84	69	9	70
26	50	16	84	49	7	79	46	29	93	58	11	78	92	15	85	69	9	80
27	64	18	82	48	5	70	71	27	96	63	6	68	82	13	81	77	16	80
28	58	18	85	56	6	70	54	29	96	72	4	63	67	21	81	79	24	82
29	53	20	87	57	14	77	61	20	94	61	10	66	60	13	82	95	14	82
30	80	20	84	59	13	76	54	11	82	52	12	69	71	15	82	69	13	72
31	50	19	81	57	18	77				58	11	70				82	14	72
	56.0	16.4	81.6	54.3	16.5	81.5	55.6	21.9	88.6 (55.0 28 days)	58.6	12.5	74.9	70.0	12.5	80.0	71.9	13.1	72.3

that oxidant maxima are directly related to the daily numbers of cardiac and respiratory deaths through the year regardless of actual temperature level. While it is true that excessive heat can kill (hence our exclusion of all days with temperature maxima above 96° F.), one cannot logically relate daily temperature maxima below 95° F. directly with the occurrence of cardiac and respiratory deaths in the Los Angeles population. It, therefore, becomes increasingly clear that oxidant *per se* is significantly related to such deaths as well as to temperature level.

It also becomes obvious that maximum allowable concentrations of total oxidant (as determined by the potassium iodide method) should not exceed 10 pphm (0.1 ppm) if the community health is not to be endangered. This is the same maximum allowable concentration established some years ago by Industrial Health experts for healthy in-plant workers, and it is the same community limit recently recom-

mended[1] by the Committee on Preventive Medicine of the Cincinnati Academy of Medicine and formally approved by the Academy Council for application to the Cincinnati area.

Careful and extensive Russian studies (Ryazanof[9]) on the toxicity of sulfur meter (0.5 mg. per m^3, or 0.2 ppm) for sulfur dioxide and 0.3 mg. per cubic meter for sulfuric acid mists.

These maximum allowable limits, now for the first time formally recommended for an American community by the medical profession, provide the

TABLE 2.—AVERAGE DAILY OXIDANT MAXIMA *VS* DAILY TEMPERATURE MAXIMA
(All L.A. Stations for 1956, 1957, and 1958)

Temp. Max.	*45–9*	*50–4*	*55–9*	*60–4*	*65–9*	*70–4*	*75–9*	*80–4*	*85–9*	*90–4*	*95–9*	*100+*
Oxidant Aver. Max.	3.75 (9)		5.76 (36)	7.19 (113)	10.19 (192)	13.28 (156)	15.33 (183)	16.88 (216)	19.36 (107)	22.43 (61)	23.78 (14)	22.00 (9)
Jan. & Feb. only	3.75 (8)		6.25 (24)	7.83 (53)	12.19 (52)	15.32 (25)	17.42 (12)	19.50 (2)	22.00	—	—	—
July & Aug. only	—		—	—	—	7.25 (4)	13.17 (23)	15.66 (85)	17.65 (43)	20.54 (26)	24.25 (4)	20.00 (1)

TABLE 3.—DAILY RESPIRATORY-CARDIAC DEATHS *VS.* DAILY AVERAGE OXIDANT MAXIMA

(1956, 1957, 1958, omitting days with Max. temp. above 96°F.)

Average Oxidant Max. (pphm)	*Resp. and Cardiac Deaths Dev. from monthly aver.*		*Taking 0–4 as zero base*
0–4	−130 (64 days)	−2.03 per day	0.00
5–9	−215 (232 days)	−0.93 " "	+1.10 per day
10–14	− 67 (299 days)	−0.22 " "	+1.81 " "
15–19	+162 (278 days)	+0.58 " "	+2.61 " "
20–24	+122 (138 days)	+0.88 " "	+2.91 " "
25–29	+104 (52 days)	+2.00 " "	+4.03 " "
30–34	+ 51 (18 days)	+2.83 " "	+4.86 " "
35–39	+ 22 (4 days)	+3.00 " "	+5.03 " "
40+	+ 8 (1 day)		
	881		
	For Jan., Feb., Mar., Apr., May (1956, 1957, 1958)		
0–4	−117.1 (53 days)	−2.21 " "	0.00 " "
5–9	− 5.3 (148 ")	−0.04 " "	2.17 " "
10–14	+ 11.3 (121 ")	+0.09 " "	2.30 " "
15–19	+ 39.8 (78 ")	+0.51 " "	2.72 " "
20+	+ 89.2 (55 ")	+1.62 " "	3.83 " "

gases and sulfuric acid mists have led to a drastic reduction in maximum allowable limits for Russian localities, and these Russian findings and recommended limits were adopted also by the Academy Council for application to the Cincinnati area. The limits recommended were 0.5 mg. per cubic air pollution engineers with definite goals to guide them in their stack and motor exhaust preventive engineering.

Summary. Bringing up-to-date his earlier studies on respiratory and cardiac deaths in Los Angeles ozone smogs (this Journal, **223**, 379, 1957), the author not only verifies the exis-

tence of almost 400 smog-correlated deaths a year in Los Angeles County but also a direct and close relationship between daily maximum temperature and ozone (or oxidant) formation in the atmosphere there. This close ozone-temperature relationship exists at temperatures ranging from 46° F. to 104° F. during the 3-year period. It is pointed out that the excess deaths on smoggy days cannot logically be considered heat deaths except at temperatures above 96° F. in Los Angeles low humidities, and therefore that the firm conclusion seems fully justified that ozone (or oxidant) smogs themselves carry community health hazards at ozone levels above 0.1 ppm. To prevent atmospheric ozone levels above 0.1 ppm it is pointed out that automobile exhaust output of unburned hydrocarbons (the major source of ozone preformers) would have to be reduced by about 85 to 90% from present levels. Tables are given of 3-year daily maximum temperatures, daily respiratory and cardiac deaths, and daily average maximum ozone (or oxidant) concentrations for all reporting Los Angeles County stations.

REFERENCES

1. Air Pollution Report: Cincinnati J. Med., **40**, 172, 1959.
2. **Borden, D. L., Waddill, J. F.,** and **Grier, G. S., III:** J. Am. Med. Assn., **128**, 1200, 1945.
3. **Ferris, E. B., Blankenhorn, M. A., Robinson, H. W.,** and **Cullen, G. E.:** J. Clin. Invest., **17**, 249, 1938.
4. **Harrison, T. R.:** Principles of Internal Medicine, Chapter 104, Disorders due to High Environmental Temperatures. New York: McGraw-Hill Book Co., 1958.
5. **Mills, C. A.:** Tr. 47th Ann. Meet. Nat. Tuberc. Assn., Cincinnati, pp. 284-290, 1951.
6. Idem: Am. J. Med. Sci., **233**, 379, 1957.
7. Idem: *In* Modern Medical Therapy in General Practice, edited by **Barr, D. P.** Baltimore: The Williams & Wilkins Company, Vol. **1**, pp. 657-694, 1940.
8. **Mills, C. A.,** and **Ogle, C.:** Am. J. Hyg., **17**, 686, 1933.
9. **Ryazanof, V. A.:** Report to Department of Community Hygiene, Central Institute of Post-Graduate Medicine, Moscow, 1957 (English translation available at Taft Sanitary Engineering Center, Cincinnati, Ohio).

(Interlingua on page 287)

MOTOR EXHAUST GASES AND LUNG CANCER IN CINCINNATI

By C. A. Mills, M.D.
PROFESSOR OF EXPERIMENTAL MEDICINE, UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO

Liquid fuel exhaust gases are today clearly recognized as the pollution source mainly responsible for ozone smogs forming in increasing densities over American urban communities. Such ozone smogs in Los Angeles have been shown to be accompanied by significant increases in respiratory and cardiac deaths on a county-wide basis (Mills[2]). Can exhaust gas damage be related more directly to those persons most exposed in urban motor traffic? Succulent plant damage has been shown to parallel such motor traffic streams: can similar damage be shown in man?

Our Cincinnati survey of 1955 was designed with this point in mind, and the survey results provided clear evidences of just such human damage. The survey's detailed data were published elsewhere[4], along with statistical handling which indicated a high degree of mathematical significance in the association between lung cancer and a) tobacco smoking, b) general urban air pollution and c) exposure to motor exhaust gases in urban traffic. Statistical handling of the survey data did not include lung cancer death rate calculations, however, since the survey covered only one person in 65 among the total living populations in the areas surveyed. The lung cancer death rates now presented must, therefore, be considered as relative and of general comparative value only, without real statistical validity under the limited circumstances prevailing in the survey.

TABLE 1.—COMPARATIVE DEATH FREQUENCIES* AMONG WHITE MALES
(By Residence Area, Age Decade, and Annual Mileage Driven)

	Polluted Basin Areas		*Suburban Areas*		*Rural Areas*	
Age Decade	*Driving Mileage*		*Driving Mileage*		*Driving Mileage*	
(years)	*<12,000*	*>12,000*	*<12,000*	*>12,000*	*<12,000*	*>12,000*
40–49	28(6%)	65(4%)	15(4%)	31(12%)	6(8%)	12(11%)
50–59	95(11%)	198(14%)	62(1%)	177(14%)	32(8%)	29(12%)
60–69	120(5%)	806(0%)	112(4%)	252(8%)	55(3%)	55(8%)
40 & over	87(6%)	172(6%)	78(2%)	121(10%)	36(4%)	29(10%)

*Deaths per 100,000 population at risk per year
Percentages of "heavy" smokers indicated in parenthesis.

Keeping these limiting factors in mind, let us inspect the tentative lung cancer death rates calculated by projecting our 1955 survey findings onto the general populations at risk. Table 1 shows such death rates among white males by age decade, by annual mileages driven, and by area of residence (for at least 10 years preceding the year of the survey). Various driving mileages were applied as the dividing line in the data handling, but clearest significance in death rate differences

were found at average driving mileages above and below 12,000 miles per year.

Table 1 and Fig. 1 (covering the same material) show in striking fashion the sharply increased lung cancer hazards associated with "heavy" exposure in urban motor traffic. Such

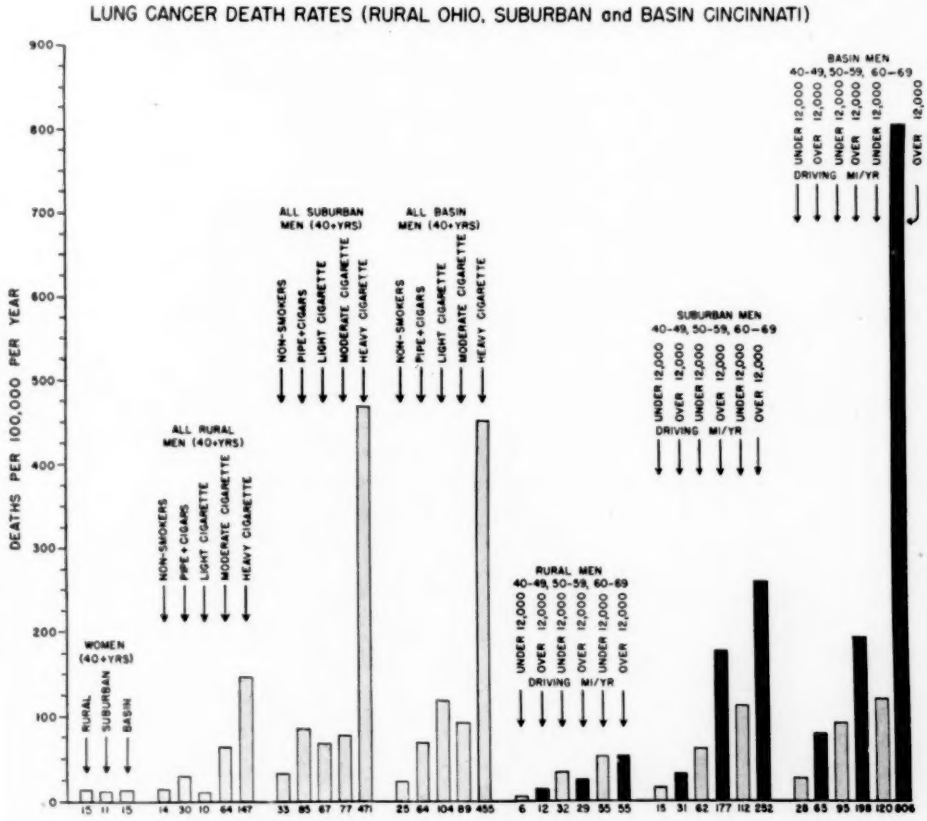

Fig. 1

driving hazards are greatest at all ages for residents of the polluted Basin areas, are slightly less for residents of cleaner suburban areas part of whose driving mileage is in the less dense suburban traffic, and are utterly lacking for residents of clean rural areas whose driving is mostly in the open country. It is illogical, therefore, to attribute the hazard to motor driving *per se*, or to attempt to link it to any factor other than the breathing of exhaust-polluted air. Rubber tire or road tar particle pollution would seem more likely to be related to vehicle speed and to provide minimal hazard in the slower-moving traffic of the Basin area. Percentages of "heavy" smokers among the living survey groups (indicated in parenthesis in Table 1) do not seem related in any consistent or significant manner to the greater lung cancer hazards of high urban driving mileages.

This association of heightened lung cancer hazards to high urban driving mileages, striking as it is here seen to be, will almost certainly become even more striking as motor traffic density worsens and human exposure to its hazards lengthens through coming decades. The survey results here pictured are based on lung cancer deaths for the 9 years from 1947 to 1955 inclusive, when such deaths were much less frequent than today and urban motor traffic far less dense. To provide clearer information on this point, we have just now brought our lung cancer survey up-to-date and found the higher lung cancer death frequencies among Basin men to be still 50% higher since the beginning of 1956 than prevailed in the nine preceding years and the slightly lower suburban frequencies to be raised by 41% (among white men of age 40 years and over). Occupational groups with high urban driving mileages (truck and taxi drivers, salesmen, and the like) and Basin residence are now second only to metal workers and railroad labor in lung cancer hazards. Curiously, workers in restaurants and bars are also up in the high-hazard class.

On the basis of the evidence at hand, it seems clearly indicated that exposure in urban motor traffic is a significant factor in lung cancer incidence, that driving mileages above 12,000 miles per year, are associated with a lung cancer hazard fully twice that of driving mileages below this level, and that this association must logically be related to the inhalation of motor exhaust products, either directly or after their atmospheric conversion to ozone or oxidant materials along the traffic stream.

The need for sharp curbs on potentially harmful motor exhaust output seems clear and unambiguous, whether we consider only the individual motor occupants exposed in the traffic stream or the major part motor exhaust gases play in the growing oxidant or ozone smog problem of urban areas today. Various evidences (Mills[3]) point to 0.1 ppm as the maximal allowable concentration for ozone or oxidant if community health is not to be endangered. Taking Los Angeles as already most deeply enmeshed in this growing urban problem, and noting that oxidant levels there have risen to as high as 1.0 ppm, it seems clear that exhaust gas (and other sources) of unburned hydrocarbons should be reduced by about 90% below presently prevailing levels of motor operation.

The proper approach to the most effective handling of this health problem would seem to be, first, the establishment by the medical profession and public health authorities of safe standards beyond which pollution of urban atmospheres should not be allowed to go, second, the translation of these maximal allowable limits into local, state, and federal legislation limiting the output *at source* of the primary polluting factors (whether they be unburned hydrocarbons or sulfur gases). The Cincinnati Medical Academy, acting through its Committee on Preventive Medicine and the Academy Council, has officially named such maximal allowable limits for local atmospheric pollution (0.1 ppm or 0.2 mg. per cubic meter for ozone or total oxidant and 0.5 mg. per cubic meter for sulfur gases) (Air Pollution Report[1]). The next step should be for Medical Academy representatives to present these safe limits to City Council for translation into the necessary control legislation, which in this case would mean the placing of limiting restrictions on primary polluting sources and a reasonable time lag for the proper engineering of compliance methods.

Certainly the health hazards now so clearly associated with the pollution of urban atmospheres seem fully ade-

quate to demand action by the medical profession and the establishment by them of safe limits beyond which such pollution should not be allowed to go. The lines of action here do not differ significantly from those applied so effectively in elimination of the black smoke palls of earlier decades. It was not then, and it cannot be now, a matter of policing individual pollution sources, but rather of legislation prohibiting the sale or operation of combustion equipment without approved safeguards for pollution control.

Summary. The Cincinnati survey of 1955 (previously reported in Cancer Research, **17**, 981, 1957) showed a high degree of mathematical significance to exist between lung cancer incidence and (1) cigarette smoking, (2) living in air-polluted or clean residential areas, and (3) driving mileages in urban traffic. Further analysis of the same basic survey data now shows the lung cancer death hazards to be greatest at all ages above 40 for drivers who are residents of Cincinnati's polluted Basin areas, slightly less for drivers residing in clean suburban areas, and utterly lacking for drivers residing far out in clean rural areas whose driving is mostly on open country roads. In general, urban residents exposed in urban traffic for over 12,000 miles per year exhibit over twice the lung cancer incidence rates of those with lesser urban driving mileages. The author recommends that the medical profession give specific recognition to these urban driving hazards and to motor exhaust gases as the dominant factor in today's increasing development of the ozone-type smogs now recognized as community health hazards at ozone concentrations above 0.1 ppm.

REFERENCES

1. Air Pollution Report: Cincinnati J. Med., **40**, 172, 1959.
2. **Mills, C. A.:** Am. J. Med. Sci., **233**, 379, 1947.
3. Idem: Cincinnati J. Med., **38**, 259, 1957.
4. **Mills, C. A.,** and **Porter, M. M.:** Cancer Res., **17**, 981, 1957.

SUMMARIO IN INTERLINGUA

Gases de Escappamento de Motores e Cancere Pulmonar in Cincinnati

Un enquete de 1955 a Cincinnati (previemente reportate in Cancer Research, **17**, 981, 1957) demonstrava un correlation de alte grados de signification mathematic inter, de un latere, le incidentia de cancere pulmonar e, del altere latere, (1) le fumar de cigarrettas, (2) le domiciliation in areas residential a aere polluite o pur, e (3) le distantias viagiate in traffico urban. Analyses additional del mesme datos fundamental ha monstrate que le hasardo del mortalitate per cancere pulmonar in omne gruppos de etate supra 40 annos es le plus alte inter motoristas qui habita a Cincinnati le polluite areas del Basin, que ille hasardo es levemente plus basse inter motoristas qui habita le minus polluite areas suburban, e que nulle tal hasardo existe del toto inter motoristas qui habita pur areas rural a grande distantias del citate e qui viagia principalmente in stratas de paisage libere. A generalmente parlar, residentes urban qui es exponite al traffico urban in plus que 12.000 millias de viage per anno exhibi plus que duo vices le incidentia de cancere pulmonar que le subjectos con plus basse totales de viage urban. Le autor recommenda que le profession medical recognosce explicitemente iste hasardos del automobilismo urban, que illo recognosce le gases de escappamento de motores como le factor dominante in le crescente disveloppamento de smog del typo a ozono del qual on sape que illo es un hasardo sanitari quando le concentration de ozono in illo es plus que 0,1 ppm.

INFLUENZA-LIKE ILLNESS IN NAVAL PERSONNEL SPRING 1959

By P. K. Fraser, M.D., Surgeon Captain, R.N.

L. A. Hatch, M.B., B.S., Dip.Bact.

L. G. H. Le Clercq, M.R.C.S., L.R.C.P., Surgeon Commander, R.N.

AND

Jill M. R. Forster, F.I.M.L.T.

(From the Department of Pathology, R. N. Hospital, Haslar, the Public Health Laboratory, Portsmouth, and the Boys' Training Establishment, H.M.S. "St. Vincent," Hampshire, England)

Studies of upper respiratory illnesses in the Portsmouth (England) Naval Command have continued since the influenza A (A2) epidemic of 1957 (Fraser, Hatch and Hughes, 1958[2]), and the outbreak of adenovirus infection of 1958 (Fraser and Hatch, 1959[3]) were observed.

An outbreak of influenza-like illness occurred in the first quarter of 1959. Serological studies revealed its multiple etiology.

Methods. Paired sera were taken in the first 10 days of illness and 2 weeks or more later from patients with upper respiratory infections admitted to hospital from the Command. The main clinical features of each patient were recorded at the bedside within 24 hours of admission. Antibiotics were not used except for the treatment of complications.

Acute and convalescent phase sera were also obtained from about three-quarters of the recruits who reported sick at a training center with an average population of 670. In addition, sera were obtained on the day of joining and 3 months later from recruits who joined this center in January and February, 1959. These sera were tested in pairs by complement fixation against antigens of influenza A, B and C, *Rickettsia burneti*, adenovirus, the psittacosis-L.G.V. group of viruses and against the streptococcus M.G. suspension in an agglutination reaction as previously described (Fraser and Hatch, 1959[3]). They were also tested against Sendai "virus particle" antigen, and, where necessary, against mumps "virus particle" antigens similar to those described by Bruce White, Gardner and Hope Simpson (1957[1]), obtained from the Standards Laboratory for Serological reagents, Colindale.

Fourfold or greater rises in titer between the first and second sera taken in acute illness were considered significant of recent infection. Those found in sera taken on joining and 3 months later at the recruit center were

TABLE 1.—ANALYSIS OF SEROLOGICAL FINDINGS IN PATIENTS ADMITTED TO HOSPITAL WITH UPPER RESPIRATORY ILLNESSES, JANUARY–APRIL, 1959

	January	*February*	*March*	*April*
No. of patients admitted	59	187	94	56
Streptococcal and Vincent's infection	14	5	10	18
Glandular fever	2	5	2	2
Number of paired sera tested	56	167	89	49
Influenza A	5	73	8	1
Influenza B	3	21	16	6
Adenovirus	3	9	16	4
Sendai		1		
Influenza A and B		4		
Influenza A and adenovirus		1		
Influenza A and B and primary atypical pneumonia		1		
Influenza B and adenovirus		1	2	
Primary atypical pneumonia	1			
Serologically negative	44	56	47	38

considered significant of infection within that period. All other titers were disregarded.

Results. From January to April, 1959, 396 patients with acute upper respiratory infections were admitted to this hospital and paired sera from 361 were tested. Table 1 shows the monthly distribution of the serological findings.

Table 2 shows the distribution of the presenting symptoms of those in hospital who had influenza A, influenza B and adenovirus infections without complications.

Of 408 boys in the recruit center who reported for treatment of respiratory illnesses, paired sera were tested from 299. The monthly distribution of these serological findings is shown in Table 3.

Of 176 serologically diagnosed patients in hospital, 32 had complications and are shown in Table 4.

Seven patients with pneumonia were seen in the recruit center. Influenza B accounted for 3, adenovirus 2, two were serologically negative and one was not tested.

In February, a girl, aged 19 years, was admitted to hospital with a history of malaise and chest pain for 2 days, and was found to have pneumonia. She died the next day. Postmortem examination showed fulminating bronchopneumonia and early rheumatic nodules on the mitral valve cusps. *Staphylococcus pyogenes* was isolated from the lung tissue and was shown to be penicillin sensitive. Influenza virus A was isolated from lung tissue and has been confirmed and designated A/England/974/59 (M. S. Pereira, personal communication).

The combined results of tests on the

TABLE 2.—ANALYSIS OF PRESENTING SYMPTOMS AND CLINICAL COURSE OF SEROLOGICALLY DIAGNOSED PATIENTS ADMITTED TO HOSPITAL WHO DID NOT DEVELOP COMPLICATIONS

Virus	*No. of Cases*	*Headache*	*Myalgia*	*Cough*	*Sore Throat*	*Mean Duration of Pyrexia (Days)*	*Mean Number of Days in Hospital*
Influenza "A"	71	57 (80%)	49 (69%)	53 (75%)	43 (61%)	3	7
Influenza "B"	37	28 (76%)	32 (86%)	22 (59%)	22 (59%)	3	7
Adenovirus	28	21 (75%)	18 (64%)	18 (64%)	19 (68%)	3	8

TABLE 3.—ANALYSIS OF SEROLOGICAL FINDINGS IN PATIENTS REPORTING WITH UPPER RESPIRATORY ILLNESSES AT THE RECRUIT CENTER (POPULATION 670) JANUARY–MARCH, 1959

	Patients Seen	*Paired Sera Tested*	*Influenza A*	*Influenza B*	*Adenovirus*	*Q Fever*	*Psitt. L.G.V.*	*Influenza A + Adenovirus*	*Influenza B + Adenovirus*	*Influenza A + Influenza B + Adenovirus*	*Adenovirus + Psitt. L.G.V.*	*Negative*
January	75	69		1	11	1	1					55
February	247	157	10	27	48			4	4	1	1	62
March	86	73		37	7		1					28
Total	408	299	10	65	66	1	2	4	4	1	1	145

paired sera taken at 3 monthly intervals, and paired acute and convalescent sera taken after reporting sick within the period from recruits who joined in January and February, are shown in Table 5.

Of those who joined in January, 52 of 61 serologically positive cases and 13 of 26 who were serologically negative reported sick with upper respiratory illnesses. Of those who joined in February, 31 of 33 who were serologically positive and 38 of 51 who were serologically negative reported with similar illnesses.

Discussion. Since the influenza A (Asian) epidemic of 1957 subsequent outbreaks of influenza-like illness have been viewed with suspicion in view of a possible reappearance of the virus with increased pneumotropism (Hers, Masurel and Mulder, 1958[4]).

Influenza A and adenovirus infections had not occurred in the last 6 months of 1958 in the hospital patients and in the last 3 months of 1958 in the recruits. No cases of influenza B were seen during 1958.

This outbreak occurred in the first 3 months of the year. Most of the cases were seen in February and by the middle of March the outbreak ended. During February there was no clinical indication that 3 or more viruses caused the illnesses seen; it appears from Table 2 that it was not possible clinically to distinguish between the 3 virus infections influenza A, influenza B and adenovirus which caused most of the illnesses. In the few cases where a tentative clinical diagnosis was made serological contradiction usually followed. Pneumonia occurred frequently in each of the 3 groups.

Paired sera taken at 3 monthly intervals at the recruit center did not reveal all the illnesses experiencd in that period; 15 of 171 tested were negative and 3 others showed rises against in-

TABLE 4.—ANALYSIS OF COMPLICATIONS IN SEROLOGICALLY POSITIVE HOSPITAL PATIENTS

	Influenza A	*Influenza B*	*Adenovirus*	*Influenza A & B*	*Influenza B + Adenovirus*	*Influenza A & B + Primary Atypical Pneumonia*
Number of proved cases	87	46	32	4	3	1
Number with pneumonia	12 (14%)	9 (20%)	4 (12%)	1	1	1
Number with sinusitis	2	–	–	–	–	–
Number with otitis media	2	–	–	–	–	–

TABLE 5.—ANALYSIS OF SEROLOGICAL FINDINGS IN BOYS WHO JOINED THE RECRUIT CENTER IN JANUARY AND FEBRUARY, 1959

Month Joined	*No. Tested*	*No. in Class*	*Influenza A*	*Influenza B*	*Adenovirus*	*Influenza A + Adenovirus*	*Influenza A + Influenza B*	*Influenza B + Adenovirus*	*Adenovirus + P.L.G.V.*	*Influenza B + P.L.G.V.*	*Influenza B + Q Fever*	*Psitt. L.G.V.*
January	87	89	6	28	9	1	2	11	0	2	1	1
February	84	87	0	16	12	0	0	3	1	0	0	1

fluenza B. All of these showed additional significant rises against one or more antigens when paired sera taken in acute illnesses within the period were tested.

Summary. An outbreak of acute upper respiratory illness occurred among naval personnel in the first 3 months of 1959. The peak incidence of cases was in February. Serological studies showed that several viruses had caused the infections. Most patients admitted to hospital had been infected by influenza A, B or adenovirus. It was not possible to distinguish clinically between these infections.

Pneumonia was the chief complication in each of these groups. One death occurred and *Staphylococcus pyogenes* and influenza A2 virus were isolated from lung tissue.

Paired sera taken at 3 monthly intervals from recruits did not reveal all the infections experienced; additional significant rises in titer against one or more antigens were found when paired sera taken in acute illness within the period were tested.

ACKNOWLEDGMENT: We are indebted to the Medical Director General of the Navy for permission to publish and to Professor A. Bradford Hill for statistical advice. The skilled assistance of Mrs. B. R. Harrison, Miss L. M. Richardson, S.B.P.O. J. E. Goodings and L.S.B.A.R. Davis was greatly appreciated.

REFERENCES

1. **Bruce White, G. B., Gardner, P. S.,** and **Hope Simpson, R. E.:** Brit. Med. J., **1**, 381, 1957.
2. **Fraser, P. K., Hatch, L. A.,** and **Hughes, K. E. A.:** J. Roy. Nav. Med. Serv., **44**, 285, 1958.
3. **Fraser, P. K.,** and **Hatch, L. A.:** Brit. Med. J., **1**, 470, 1959.
4. **Hers, J. F. P., Masurel, N.,** and **Mulder, J.:** Lancet, **2**, 1141, 1958.

SUMMARIO IN INTERLINGUA

Un Morbo Influenzoide in Personal Naval in le Primavera del Anno 1959

Un eruption de acute morbo supero-respiratori occurreva in personal naval durante le prime 3 menses del anno 1959. Le incidentia habeva su culmine in februario. Studios serologic monstrava que le infectiones esseva causate per plus que un virus. Le majoritate del patientes admittite al hospital esseva inficite per virus de influenza A, virus de influenza B, e adenovirus. Il non esseva possibile establir un differentiation clinic inter le infectiones causate per ille agentes.

Pneumonia esseva le complication principal in omne le gruppos. Un morte occurreva. *Staphylococcus pyogenes* e virus de influenza A2 esseva isolate ab le tissus pulmonar de iste patiente.

Pares de specimens de sero, obtenite ab le recrutas con un intervallo de 3 menses, non revelava omne le infectiones experientiate. Significative augmentos additional del titros contra un o plures del antigenos esseva trovate quando pares de specimens de sero esseva obtenite e testate durante maladia acute intra le periodo mentionate.

PRIMARY ALDOSTERONISM, OBSERVATIONS ON 2 CASES

By Felix Cortes, M.D.*
RESIDENT IN MEDICINE

Charles R. Shuman, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

AND

Bertram J. Channick, M.D.
INSTRUCTOR IN MEDICINE

(From the Department of Medicine, Temple University Medical Center, Philadelphia, Pennsylvania)

Among the main features of primary aldosteronism as described by Conn[5] are: 1) hypertension, 2) intermittent muscular weakness and partial paralysis, 3) tetany and paresthesia, 4) polyuria with alkaline urine, 5) inability to concentrate urine upon withholding fluid or after Pitressin administration, 6) hypokalemia due to renal potassium wastage, 7) tendency to hypernatremia, alkalosis, and elevation of carbon dioxide-combining power. These metabolic abnormalities are produced by the action of a potent mineralo-corticoid hormone, aldosterone, secreted by adrenocortical cells. The function of this hormone appears to be that of regulating the metabolism of sodium and potassium. Overproduction of aldosterone by an adrenal tumor or by a hyperplastic gland results directly in the increased retention of sodium in body fluids with the concomitant loss of potassium. The disturbance in electrolyte balance within cells and body fluids has far-reaching consequences resulting in the renal, neurologic, muscular and vascular abnormalities which comprise the syndrome.

The recognition of aldosteronism as the cause of hypertension has been reported in 26 cases (Barrett, Boyliss and Rees[1], Bartter and Biglieri[2], Campbell, Nicolaides and Steinbeck[3], Chalmer *et al.*[4], Conn[5], Conn and Lonis[6], Crane, Short and Petersen[7], Crane, Vogel and Richland[8], Eales and Linder[9], Fine *et al.*[10], Foye and Feichtmeir[11], Goldsmith *et al.*[13], Hellem[15], Hewlett *et al.*[16], Holten and Petersen[17], Hudson, Barnett and Bornstein[18], Kretchmer, Dickinson and Karl[19], Mader and Iseri[20], Mellinger *et al.*[21], Milne, Meuhreke and Avid[22], Ortuzar, Thomsen and Gonzolez[24], Scarce and Whitstone[25], Sayer and Eyre[26], Skavse *et al.*[27], von Buchem, Doorenbos and Elings[28]) in the medical literature. Not all of these have manifested the features of the clinical syndrome as described. Indeed, one of the points stressed in the early cases was absence of edema which has subsequently been demonstrated in 3 patients (Fine *et al.*[10], Hewlett *et al.*[16], Sayer and Eyre[26]) and was noted in one of the cases reported here. Additional findings such as diarrhea occurring at the time of acute symptoms, menorrhagia, diabetes and abnormal flocculation tests have been observed in several patients. Despite the variability of presenting complaints, the

*Present address: U.S. Naval Hospital, Portsmouth, Virgina.

majority of the cases have been found to be due to adenoma (aldosteronoma); adrenocortical hyperplasia was present in 4 cases, and in 2 an adrenal carcinoma was found.

In this report, 2 patients with primary aldosteronism are described in whom the clinical features were somewhat atypical. The first patient was entirely asymptomatic except for hypertension until she became comatose during a bout of diarrhea; the second was treated for recurrent edema and was admitted for study as to the cause of menometrorrhagia. In each, the diagnosis was suspected on the basis of laboratory findings and confirmed by demonstration of large amounts of aldosterone in urine and by radiological studies using retroperitoneal CO_2 insufflation.

Case Reports. CASE 1. Mrs. H.N. a 43-year-old Negro woman was admitted to Temple University Hospital on July 16, 1957 with a history of diarrhea, fever, and vomiting of 36 hours' duration. The onset of the diarrhea was gradual but progressive with bowel movements every 30 minutes. Vomiting was described as mild to moderate. On the day of admission the patient was found to have high fever; she was disoriented and confused, and was referred after being treated with paregoric and oral antibiotics.

Past medical history revealed hypertension for 5 years, and renal disease for 3 years. She had been treated with a strict salt-free diet and Ansolysen 80 mg. per day with control of the blood pressure around 190/100. She also revealed a history of acute rheumatic fever at the age of 20.

Temperature 103.5° F. pulse 90 per minute. The physical examination on admission revealed a well nourished and developed Negro woman, semi-stuporous and very restless. The blood pressure was unobtainable. The eyeballs were sunken, the mucous membranes were dry, and there was loss of the normal skin turgor. The lungs were clear to percussion and auscultation. Examination of the heart revealed the point of maximal intensity at the 5th intercostal space and midclavicular line; sinus rhythm was 90 per minute; A_2 was louder than P_2; a grade 2 soft apical systolic murmur was present. In the abdomen marked hyperperistalsis was found. Neurologic examination revealed normal findings. The patient was admitted with a diagnosis of acute gastroenteritis and electrolyte imbalance, probably hyponatremia.

The initial treatment consisted of intravenous fluids for hydration, Levophed, atropine sulphate, and oxygen by nasal catheter.

The initial laboratory studies revealed a serum sodium of 147 mEq. per L., chlorides of 98 mEq. per L., potassium of 2.5 mEq. per L. Initially the treatment consisted of 5% glucose in water and because of the history of renal disease and the presence of oliguria the patient was given only 52 mEq. of potassium chloride intravenously over the first 12 hours. At this time the patient was treated without the use of vasopressor agents and the urinary output increased to normal. After 24 hours a total of 130 mEq. of potassium chloride had been administered intravenously; the patient had regained consciousness, was able to take fluids and potassium chloride by mouth.

The patient continued to improve gradually, but her serum potassium remained below normal levels. Potassium chloride in dosages of 4 gm. per day was continued, in addition to a diet containing 3.8 gm. of potassium. On July 17, 1957, her serum potassium was 4.7 mEq. per L., and the supplementary potassium was discontinued. During her hospital course the blood pressure reached levels up to 200/120 and was constantly above normal levels. The urine, showed a low specific gravity, alkaline reaction, a trace of albumin and pyuria on repeated occasions. Because of the refractory hypokalemia and the high normal serum sodium levels an aldosterone secreting tumor was suspected. However, she denied weakness, numbness, paresthesias or symptoms suggestive of hypokalemia. Marked polyuria and polydypsia had been present for some time.

Laboratory Studies. The Fishberg concentration test showed a maximum concentration of 1.014, the intravenous PSP test showed, at 15 minutes, 2.7% excretion; at 60 minutes, 19.8% excretion, and the urea clearance was 59 mg. per 100 ml. average on one occasion and 25 mg. per 100 ml. on another. The glucose tolerance test was as follows: fasting 120 mg. per 100 ml., 1 hour 176 mg. per 100 ml., 2 hours 193 mg. per 100 ml. and 3 hours 176 mg. per 100 ml. A 24-hour urine test for 17-ketosteroids was 7.5 μg. Urinary corticosteroids per 24 hours was 122 μg. and serum pH 7.50 and 7.52.

Electrolyte balance studies were carried out on several occasions (see Table 1). Presacral

CO_2 study was performed and revealed an enlarged left adrenal gland. Urine assays for aldosterone revealed 80 μg. per 24 hours (normal being between 4 and 10 μg. secretion per 24 hours).

On the day prior to the operation the patient was given 4 gm. of potassium chloride by mouth and 4 gm. of potassium intravenously in addition to the diet. On August 30, 1957, under endotracheal anesthesia a thoracoabdominal approach to the left adrenal gland was carried out via the extrapleural approach, and after the resection of the 10th rib the peritoneal cavity was entered. The right adrenal gland was palpated and found to be normal. On palpation of the left adrenal gland, its upper pole was thicker and firmer than the remainder of the gland. It was found to contain a tumor mass approximately 3 cm. in diameter. The left adrenal gland was removed intact. A renal biopsy was performed.

The patient was returned to the ward in good condition. During the first 24 hours postoperatively, the patient received 211 mEq. of potassium intravenously. Her general condition was good, she was mentally clear and taking food by mouth. On August 31, 1957, electrolyte studies were performed and reported as follows: Sodium, 137 mEq. per L.; chlorides, 95 mEq. per L.; potassium 1.8 mEq. per L. At 1:00 P.M. the same day and before the electrolytes were reported, the patient was found to be unconscious, the blood pressure was unobtainable, temperature was 104° F., there was marked generalized flaccidity and areflexia. An electrocardiogram was performed and showed sinus tachycardia, marked prolongation of the QT interval, flat-

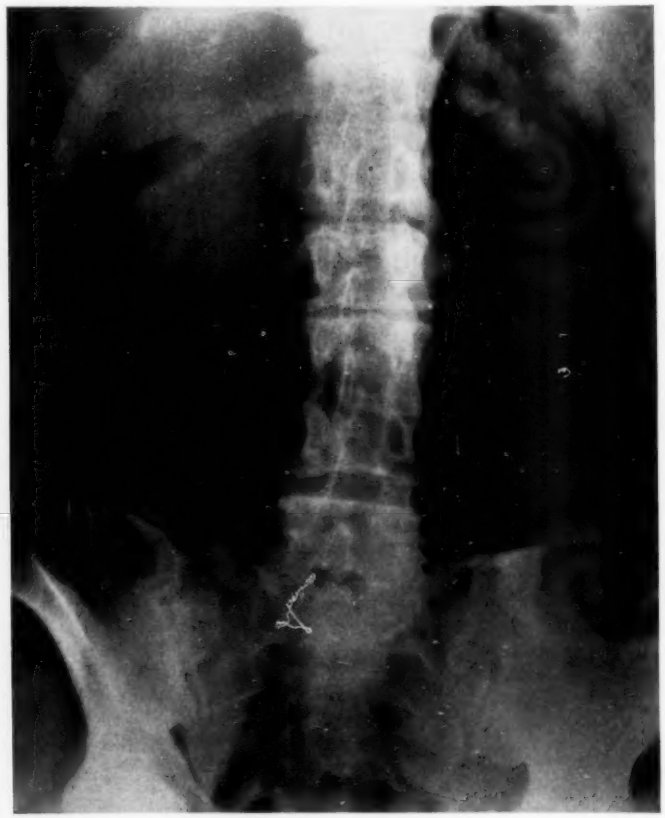

Fig. 1.—Case 1. Retroperitoneal carbon dioxide study showing enlargement of the left adrenal gland.

tening of the T wave with depression of the ST segments. This was interpreted as being compatible with hypokalemia. She was treated with intravenous fluids, Levophed, Chloromycetin, isotonic solution of potassium chloride (11.2 gm. of potassium chloride per 1,000 ml. of distilled water). Hydrocortisone 300 mg. per 24 hours was also administered because of the possibility of adrenal insufficiency due to suppression of the contralateral adrenal gland. At 9:00 P.M. the temperature was 104° F. The blood pressure was being maintained with Levophed. The patient was still comatose, but with good urinary output. The serum potassium was 3.8 mEq. per L., serum sodium was 135 mEq. per L.; the electrocardiogram was compatible with marked hypokalemia. *September 1, 1957, at 8:00 A.M.:* The urine output was 4,000 ml. and the patient's condition was unchanged. She developed numerous bullae over the skin of the chest, both anteriorly and posteriorly. During the last 24 hours the patient received 764 mEq. of potassium and 77 mEq. of sodium intravenously. An electrolyte study done on the same morning revealed the following: Serum sodium, 136 mEq. per L.; serum potassium, 2.8 mEq. per L.; blood urea nitrogen, 17 mg. per 100 ml. Urinary electrolytes were as follows: Sodium, 20 mEq. per L.; chlorides, 18 mEq. per L.; and potassium was reported as negligible even in undiluted urine. Urinary aldosterone determination, 3 μg. per 24 hours. Tracheotomy was performed for removal of secretions and to improve ventilation. Serum electrolytes showed sodium of 138 mEq. per L.; potassium of 6.7 mEq. per L. and an electrocardiogram done at this time still showed evidence of hypokalemia.

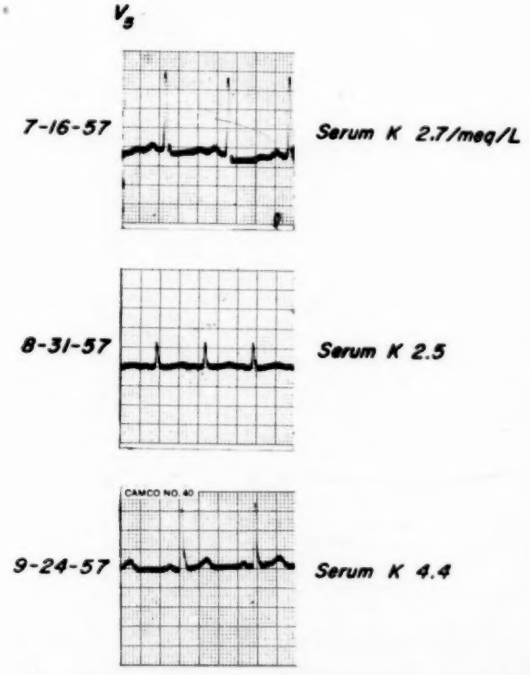

Fig. 2.—Case 1. Electrocardiogram showing changes compatible with hypokalemia. On September 24, 1957 electrocardiogram showed normal configuration.

September 2, 1957 at 8:00 A.M.: Urine output was 3,000 ml. Potassium and sodium administration were 734 mEq. and 38 mEq. respectively intravenously in 24 hours. The patient was much improved. She was conscious with a blood pressure of hypertensive levels, around 200/120. Serum electrolytes at this time were: sodium of 143 mEq. per L.; potassium of 4.2 mEq. per L. The urine electrolytes were: sodium, 21 mEq. per L.; potassium, negligible. Because of the hypertension hydrocortisone was reduced to 100 mg. for the next 24 hours, and then was dis-

continued. The patient remained afebrile for the rest of the day. *September 3, 1957:* The blood pressure was still quite elevated to 240/100. The physical examination revealed coarse rales at both bases. Tachycardia of 120 per minute was present. There were numerous large bullae over the anteroposterior chest and the upper extremities. These bullae were attributed to the hyperpyrexia, alcohol bath for cooling and to acute transient adrenal insufficiency.

The patient continued to improve and intravenous potassium was discontinued after a total intake of 1,800 mEq. of potassium and 213 mEq. of sodium over a 76-hour period. In spite of the low sodium intake the patient was able to maintain normal serum levels. The patient was found to have pneumonitis of the left base which was treated successfully with antibiotics. The remainder of the patient's postoperative course was uneventful. The blood pressure gradually dropped to

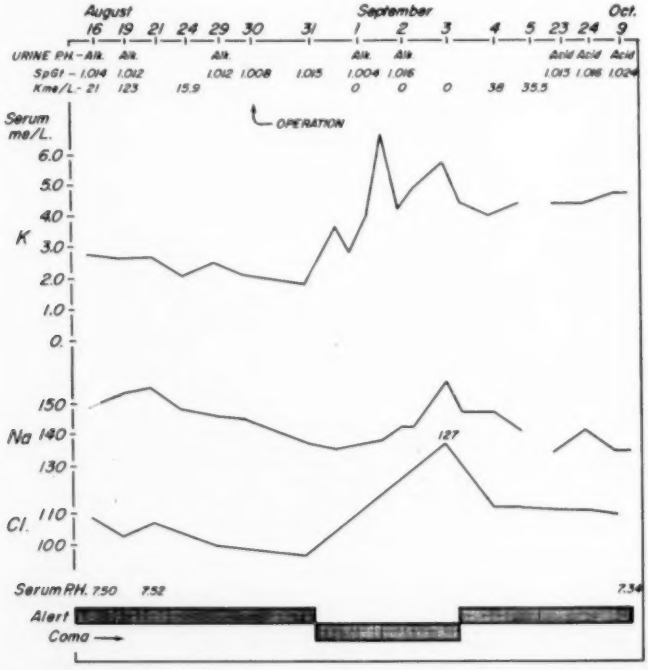

Fig. 3.—Case 1. Urinary findings and serum electrolytes. Note the negligible urinary potassium excretion with serum levels of 6 mEq. per L.

Fig. 4.—Case 1. Adenoma of the left adrenal gland.

levels around 140/90. The urine specific gravity gradually rose to 1.015 and then 1.019 with an acid reaction. Serum electrolytes remained normal even after discontinuance of supplementary potassium. A 2-hour postprandial sugar done after the administration of 100 gm. of glucose was 89 mg. per 100 ml. power was 51 volumes %. Two hours postprandial sugar was 87 mg. per 100 ml. and the serum pH was 7.34.

The patient was readmitted on June 1, 1958, for re-evaluation and at this time she stated that the polyuria and polydypsia were no longer present. The blood pressure ranged

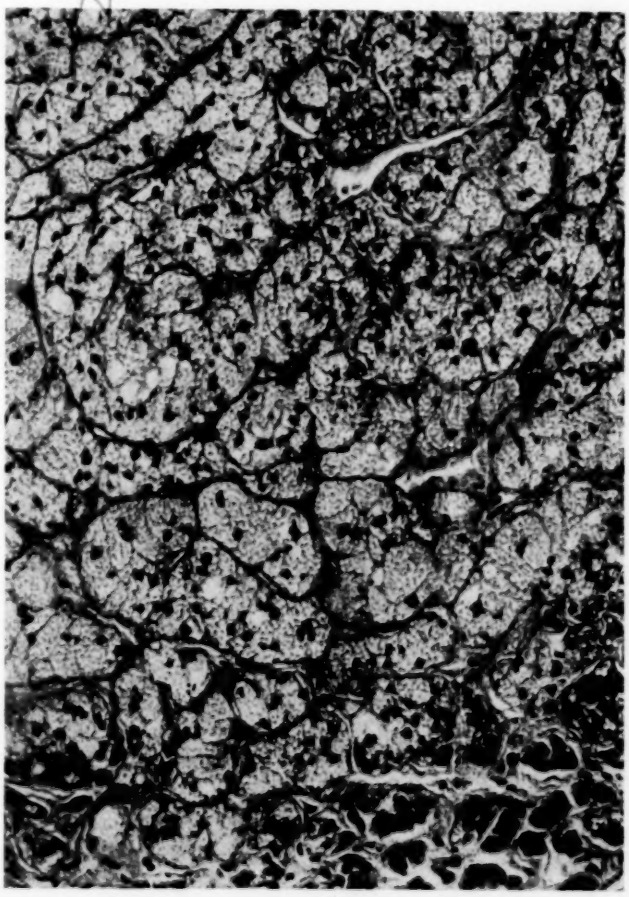

Fig. 5.—Case 1. Histopathology of adrenocortical adenoma. Cell types representative of the three zones of the adrenal cortex are noted.

Phenolsulfonphthalein test at 15 minutes showed 13% excretion, 1 hour showed 33% excretion.

Two months after her discharge the patient was asymptomatic. The urinalysis showed specific gravity of 1.024 and acid reaction. The blood pressure was 140/90. The serum sodium was 134 mEq. per L.; serum potassium was 4.7 mEq. per L.; CO_2-combining between 130/70 and 150/90 mm. Hg respectively.

Laboratory Studies. The urinalysis revealed a 1.022 specific gravity, an acid reaction and was negative for protein and sugar. A 2-hour postprandial blood sugar was 88 mg. per 100 ml. Serum potassium, 4.5 mEq. per L. and 5.2 mEq. per L.; chloride, 109 mEq. per L. and 112 mEq. per L.; CO_2 content 21

mEq. per L. or 48 volumes %. An attempt at a kidney biopsy was unsuccessful.

Several months after the attempt at right renal biopsy the patient began to notice some darkening of the skin. She also experienced nervousness, anorexia and episodes of nausea and at times vomiting. She was admitted to the hospital with the diagnosis of possible adrenal insufficiency. The following are the results of the studies done at this time:

Urinalysis revealed an acid reaction, specific gravity of 1.010 and no albumin. Serum electrolytes: Sodium, 142 and 146 mEq. per L.; potassium 5.6 and 6.1 mEq. per L.; chloride, 100 and 104 mEq. per L.; CO_2, 15 mEq. per L.; calcium, 10.2 mEq. per 100 ml. and blood urea nitrogen 25 mg. per ml. An analysis of the 24-hour collection of urine showed: 17-ketosteroid excretion, 2.1 mg. per 24 hours and corticoid excretion 20 μg. per 24 hours. An adrenal stimulation test was carried out by administering 40 units of ACTH daily for 3 consecutive days. The following were the hormone excretion levels in the urine: 17-ketosteroid, .79 mg. per 24 hours, and corticoid, 7 μg. per 24 hours.

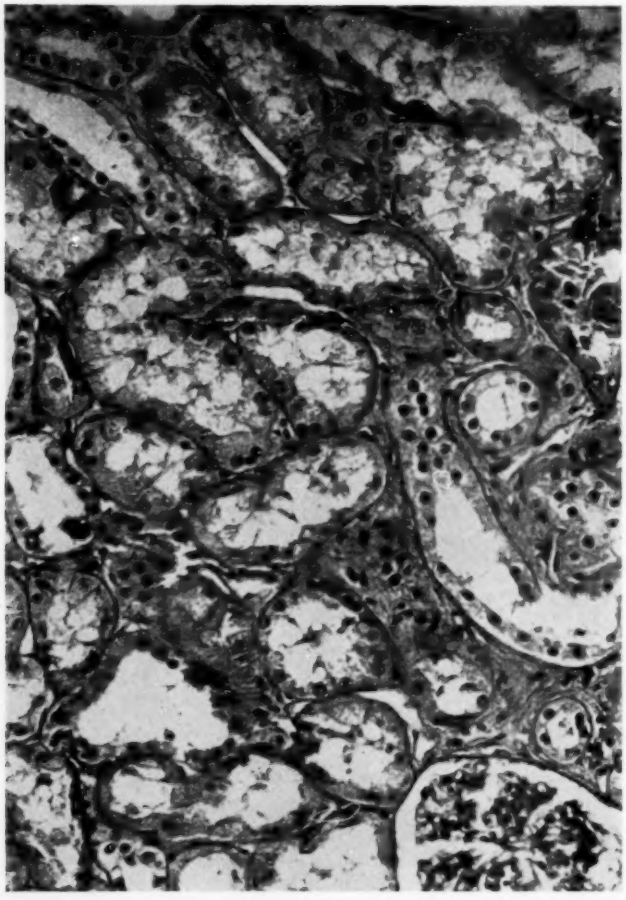

Fig. 6.—Case 1. Kidney biopsy showing changes consistent with kaliopenic nephropathy and chronic glomerulonephritis.

The diagnosis of adrenal insufficiency was verified and the patient was started on replacement therapy with 37.5 mg. of cortisone and 4 to 10 gm. of sodium chloride daily. On this regimen she has been asymptomatic for the past 4 months.

COMMENT. The noteworthy features in this case are the absence of symptoms prior to prostration and coma associated with severe diarrhea and vomiting. Because of hypertension, she had followed a low salt diet intake for 5 years and a low sodium level in the serum was anticipated. Surprisingly, a high level was found with subnormal urinary potassium excretion (these findings were checked in two laboratories). Despite potassium replacement during the preoperative period, acute hypokalemic symptoms appeared within 24 hours postoperatively. A total retention of 1679 mEq. of potassium during the next 72 hours was calculated. The development of postoperative circulatory collapse and coma is understandable in view of this extreme degree of potassium depletion. The earlier absence of symptoms is inexplicable especially in view of the potassium supplements employed preparatory to operation.

The diabetic glucose tolerance curve preoperatively became normal following recovery from the postoperative complications. It is possible that intensive hypokalemia and tissue potassium depletion interferes with glucose utilization and glycogen deposition. The production of diabetic glucose tolerance curves in experimental animals by prolonged potassium depletion has been established. Correction of cellular potassium deficits restore carbohydrate utilization to normal (Furman[12], Gudner *et al.*[14]). On the other hand, the possibility of an anti-insulin effect of aldosterone has to be considered. The glucocorticoid properties of this steroid factor are negligible but may become significant with prolonged hypersecretion of the hormone.

TABLE 1.—CASE 1. ELECTROLYTE BALANCE STUDIES: PRE- AND POSTOPERATIVE

	Intake			Output									Balance		
				Gastric			Urinary			Ins.	Total				
Date	Vol. ml.	Na*	K*	Vol.	Na*	K*	Vol.	Na*	K*	Vol.	Vol.	Na*	K*	Vol.	Na*	K*
8/16		82	96					126	50			126	50		+44	-46.2
8/19		82	96					30	25			30	25		+52	+ 71
8/30	4300	98	107	Operation							3965			+335	?	?
8/31	5000	77	764	900	38	10	2925	64	0	2000	5825	100	10	-825	-23	+754
9/1	6650	38	734	200	8	4	4300	91	0	1500	6060	99	4	+650	-61	+730
9/2	4435	0	195	0			1800	24	0	1300	1500	24	0	+135	-24	+195

* mEq.

Total K intake 8/31 - 9/2 = 1693 mEq.
Total K output 8/31 - 9/2 = - 14 mEq.
Positive K balance +1679 mEq.

The development of adrenal insufficiency 1½ years after unilateral adrenalectomy suggests that something happened to the remaining adrenal gland. Certainly the fact that she was able to do well for one year after the operation and without evidences of adrenal insufficiency suggests that perhaps the second unsuccessful attempt at a right kidney biopsy resulted in some injury to the remaining right adrenal gland.

CASE 2. Mrs. H.S. a 48-year-old white woman was admitted to Temple University

Hospital because of menometrorrhagia of 4 months' duration. Hypertension had been noted in 1951. In 1954, the blood pressure was found to range consistently from 190/95 to 200/100 and she was given reserpine in treatment for this condition. The patient had experienced premenstrual edema during the past 4 years for which she has been treated with Diamox and mercurial diuretics. The Diamox was discontinued because of weakness. She received an injection of meralluride every 2 to 3 weeks in order to control her edema. Following the injection, the patient noted episodes of severe weakness, numbness of the extremities and paresthesias. On one occasion after a mercurial injection she was unable to get out of bed because of marked weakness. On another occasion she had to be assisted into her house due to extreme muscular weakness.

The blood pressure was 230/130, pulse 78 per minute and the temperature 98.4° F.

The physical examination revealed a well nourished white woman in no apparent distress. There was flushing of the face and neck. Funduscopic examination showed grade 2 constriction of the arterioles. The heart: the point of maximal intensity was forceful and diffuse at the 6th intercostal space and 1 cm. to the left of the midclavicular line. A split M., and a grade 2 apical systolic murmur were present. The abdomen was nontender and no masses or organs were palpable. No edema of the legs was noted. The neurological examination was normal as was the pelvic examination.

Laboratory Studies. The urinalysis (on three occasions) revealed an alkaline reaction, specific gravity 1.007 to 1.012, and a trace of albumin was present in one specimen. A Fishberg concentration test, 1.012 maximum; blood urea nitrogen, 10 mg. per 100 ml.; 2-hour post-prandial blood sugar, 88 mg. to 114 mg. per 100 ml. The electrolytes were as follows: Serum sodium, 147 and 150 mEq. per L.; potassium, 2.2 and 2.5 mEq. per L.; chloride, 101 and 99 mEq. per L.; CO_2 content, 34 and 36 mEq. per L.; serum pH, 7.41 and 17-ketosteroids, 9.6 mg. per 24 hours. The corticosteroids were 160 μg. per 24 hours and aldosterone, 22.4 μg. per 24 hours.

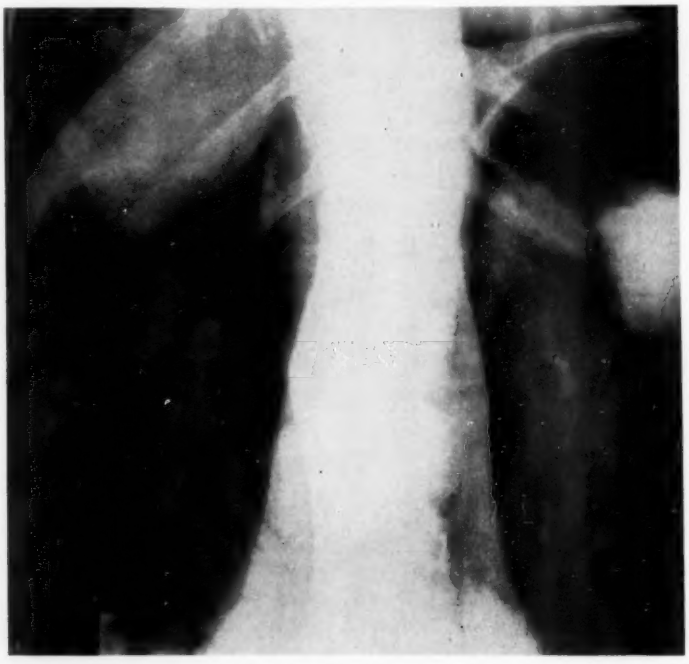

Fig. 7.—Case 2. Retroperitoneal carbon dioxide studies showing enlargement of the left adrenal gland.

An electrocardiogram disclosed the following: Left ventricular hypertrophy, prolongation of the QT interval, flattened T waves and prominent U waves. This was interpreted as myocardial disease or due to an electrolyte disturbance, that is, hypokalemia.

A retroperitoneal CO_2 study was performed and both adrenals were visualized. The left adrenal gland appeared to be enlarged.

On April 19, 1958, under endotracheal anesthesia the left adrenal gland was removed which showed a 1 × 1 cm. tumor.

The preparation for surgery consisted of supplementary potassium chloride orally and intravenously. Hydrocortisone was added to the intravenous solution used during the operative period and for 24 hours following surgery. A total of 404 mEq. of potassium was administered.

During the first 24 hours postoperatively the patient developed oliguria, followed by a marked diuresis during the second 24 hours after surgery. Her blood pressure was relatively normal during the early postoperative period but this was followed by a rise to preoperative levels and then a gradual return to lower levels as cortisone was discontinued.

The endometrial biopsy obtained at the time of adrenalectomy showed "atypism" and because of the fear of carcinoma of the endo-

Fig. 8.—Case 2. Left adrenocortical adenoma.

TABLE 2.—CASE 2. SUMMARY OF PRE- AND POSTOPERATIVE STUDIES. THERAPY ADMINISTERED POSTOPERATIVELY

	4/14/58	4/15/58	4/16/58	4/19/58		4/20/58		4/21/58		4/23/58
Serum		pH.7.41		8:00 A.M.	3:00 P.M.	8:00 A.M.	3:00 P.M.	8:00 A.M.	3:00 P.M.	
Na mEq/l	150	147		150	142	146	143	147	145	144
K mEq/l	2.2	2.5	2.3	3.0	3.7	2.5	2.8	3.2	4.1	3.6
Cl mEq/l	101	99		98				102		
CO_2mEq/l	37	36				31		31		
Urine										
Na mEq/l			49		162		Negligible		20	
K mEq/l			22.4		63.8		6.4		6.1	
Cl mEq/l			45							
Vol. cc.	3025	1900	1350	12hours 524	12 hours 200	2260		1685		
Reaction	Alk.	Alk.	Alk.			Acid				Acid
Sp.Gr.	1.012	1.013	1.007			1.020				

THERAPY

	4/18/58	4/19/58	4/20/58	4/21/58	Total
Potassium intake	147 mEq. and diet	110 mEq. (8.2 Gm.KCL)	240 mEq. (18.2 Gm.KCL)	54 mEq. and diet	404 mEq. K+
Cortisone	50 mg. I.V.	150 mg.	200 mg.	50 mg. and 30 u. ACTH	
Sodium	Diet	0	0	Diet	0 Supplement

metrium a hysterectomy, bilateral salpingo-oophorectomy and an appendectomy were carried out on April 29, 1958.

Follow-up studies have shown normal electrolytes, an acid urine, and reversion of the electrocardiogram to normal. The blood pressure remains around 140/80 mm. of Hg. The amount of aldosterone in the urine is within normal limits.

COMMENT. The diagnosis of aldosteronoma was suspected on the basis of low specific gravity and alkaline reaction of the urine in a hypertensive patient. Further confirmation was obtained immediately by the electrocardiogram and then by the low serum potassium and elevated CO_2-combining power noted in serum electrolyte studies. Conclusive proof was gained by retroperitoneal CO_2 insufflation which demonstrated a left adrenal mass. The urine excretion of aldosterone was found to be abnormally high.

In this instance, the clinical features of Conn's syndrome were elicited. However, edema was a significant element of the history, the treatment of which with diuretics induced the classical symptoms. The explanation for edema in this instance is not apparent. It is possible that it was pre-menstrual in type and not directly related to the adrenal tumor.

As in the first case, oliguria was noted during the initial 24 hours postoperatively, and this was followed by the same profound polyuria of relatively high sodium content and virtual absence of potassium. Despite hypokalemia, the urinary potassium levels were lowest at this period. There appears to be an active, rapid potassium transfer into cells and a release of sodium resulting from the removal of aldosterone activity. Finally, the endometrial hyperplasia and menometrorrhagia observed in this case may be related in some way to the high levels of aldosterone. During the past 6 months this patient has been found to have normal blood pressure and has felt entirely well. It is noteworthy that edema has not recurred, suggesting that hyperaldosteronemia was responsible for it.

Discussion. The alterations in renal function found in these cases were consistent with those described previously. There was no evidence of change in the rate of glomerular filtration. Tubular function, however, was seriously disturbed as evidenced by failure to concentrate urine, inability to produce an acid urine, and impairment in phenolsulfonphthalein excretion. It was the presence of a low specific gravity and an alkaline urine which suggested the diagnosis of aldosteronism in the second patient. Urinary electrolyte excretion was reduced in both patients. It was felt that urine sodium values were lowered by the increased reabsorption produced by the action of excessive aldosterone. The low levels of urinary potassium may be the end result of prolonged depletion of body potassium. This view is supported by the large quantity of potassium needed to achieve repletion during the postoperative period.

The alkalinity of urine cannot be attributed to excessive potassium excretion in these cases as was suggested in previously reported instances. Inability to produce an acid urine appears to be due to a direct effect of the hormone upon renal tubular function rather than hypokalemic damage to the tubular cells. This is suggested by the rapid recovery of the capacity to form an acid urine after removal of the adrenal tumor. Perhaps inhibition of carbonic anhydrase by the hormone or by the intracellular electrolyte alterations due to hormone action, limits the production of hydrogen ions available for excretion by the tubules.

The recovery of concentrating power of the kidney is comparatively slow. It

is likely that the cytostructural changes associated with kaliopenic nephropathy are related to this impairment. As tubular damage is repaired, the concentrating capacity is re-established over a period of 10 to 14 days. The renal lesion demonstrated in the first case is similar to that described by Conn and by other investigators studying the effects of hypokalemia upon renal function and histopathology. In addition to degenerative tubular changes persistent hypopotassemia is associated with a high incidence of pyelonephritis.

Speculation upon the pathogenesis of aldosterone tumors is premature at this time. The possibility exists, however, that prolonged sodium restriction provides a stimulus for the secretion of a hypothalamic neuro-humor which increases the rate of production of aldosterone (Nicholson[23]).

Long term stimulation of the aldosterone producing cells may lead to adenoma formation in a manner similar to the production of nodular thyroid hyperplasia in chronic iodine deficiency. Functional activity of adrenal adenomata is presumed to be present in only a small percentage of these lesions, just as in the case of thyroid adenomata.

The extent of potassium depletion in Case 1 may have approximated one-third of the total exchangeable potassium estimated for a normal woman of this body size. The pre-operative potassium replacement apparently failed to achieve adequate tissue levels despite transient elevations of serum potassium to low normal values. During this period, potassium excretion remained low. Administration of potassium during surgery was insufficient to prevent an extreme reduction of serum levels to the point where peripheral circulatory collapse and coma supervened. Intensive potassium therapy, using isotonic (1.12%) potassium chloride solution, resulted in a return of serum levels to normal and aided in her recovery. At the same time, Levophed and hydrocortisone were infused in order to support the failing circulation. In retrospect, a longer period of more vigorous potassium replacement and low sodium diet might have prevented the reaction observed postoperatively. A guide for adequate preparation may be the return to increased levels of urinary potassium during the pre-operative period.

The diagnosis of functioning aldosteronoma may be suspected in the following situations: 1) the presence of Conn's syndrome, 2) hypertensive patients exhibiting a fixed low specific gravity and alkaline urine, 3) an electrocardiogram exhibiting changes of hypopotassemia otherwise unexplained, 4) the presence of an unexplained hypokalemic alkalosis.

The diagnosis may be confirmed by the demonstration of an adrenal lesion using the retroperitoneal CO_2 insufflation technique with simultaneous intravenous pyelography. Further conclusive evidence supporting the diagnosis is provided by the determination of urinary aldosterone hyperexcretion. A recent suggestion of merit is that of observing the effect of administration of aldosterone antagonists upon urinary electrolyte excretion patterns. In aldosteronoma, the antagonist will reverse the low sodium:potassium ratio indicating the previous aldosterone effect. Another important place for the aldosterone antagonist would be in preparation for surgery, whereby an attempt would be made to reverse the effects of the hormone and thus to correct the characteristic potassium deficit.

Summary. Two patients with primary aldosteronism due to aldosteronoma have been encountered during the past

year. The clinical features manifested by these patients were entirely dissimilar and did not coincide with the syndrome described in many of the published cases. The first patient, a 45-year-old Negress under treatment for hypertension for 5 years at another hospital, was admitted in a state of peripheral circulatory collapse following an acute episode of diarrhea. Hypokalemia, attributed initially to diarrhea, proved resistant to therapy with potassium administration over a period of several weeks. She disclaimed any symptoms of weakness, paralysis, or tetany prior to admission. The second patient, a 50-year-old white woman, was admitted for treatment of menorrhagia. Hypertension and edema had been under treatment for 4 years. On two occasions, the administration of diuretics had resulted in brief episodes of extreme muscular weakness. In both cases, retroperitoneal CO_2 insufflation demonstrated an enlargement of the left adrenal gland. Twenty-four-hour urine specimens revealed elevated aldosterone levels (80 μg. and 24 μg., respectively) with normal 17-ketosteroid and 11-oxysteroid excretion. Surgical removal of the adrenals in both cases revealed almost identical adenomas. Large amounts of potassium salts were required to maintain normal serum levels of this electrolyte during the operative period. Post-operatively, the blood pressure declined to shock levels in one case and to normal in the other; in both, there was a transient period of hypertension during cortisone administration after operation. Abnormal glucose tolerance tests reverted to normal after recovery.

The development of adrenal insufficiency in one case was probably due to trauma from an unsuccessful attempt at renal biopsy one year after the removal of the opposite adrenal gland. Replacement therapy has successfully controlled this complication.

REFERENCES

1. **Barrett, P. K. M., Boyliss, R. I. S.,** and **Rees, J. R.:** Proc. Roy. Soc. Med., **51,** 720, 1955.
2. **Bartter, F. C.,** and **Biglieri, E. G.:** Ann. Int. Med., **48,** 6, 47, 1958.
3. **Campbell, C. H., Nicolaides, N.,** and **Steinbeck, A. W.:** Lancet, **2,** 553, 1956.
4. **Chalmer, L. M., Fitzgerald, M. G., James, A. H.,** and **Scarborough, H.:** Lancet, **1,** 127, 1956.
5. **Conn, J. W.:** A.M.A. Arch. Int. Med., **97,** 135, 1956.
6. **Conn, J. W.,** and **Lonis, L. H.:** Ann. Int. Med., **44,** 1, 1956.
7. **Crane, M. G., Short, G.,** and **Petersen, J. E.:** Am. J. Med., **24,** 313, 1958.
8. **Crane, M. G., Vogel, P. J.,** and **Richland, K. J.:** J. Lab. & Clin. Med., **48,** 1, 1956.
9. **Eales, L.,** and **Linder, G. C.:** Quart. J. Med., **25,** 539, 1956.
10. **Fine, D., Musilas, L. E., Colskey, J.,** and **Oxenhorn, S.:** New England J. Med., **256,** 147, 1957.
11. **Foye, L. D., Jr.,** and **Feichtmeir, L. D.:** Am. J. Med., **19,** 966, 1955.
12. **Furman, F. A.:** Am. J. Physiol., **167,** 314, 1951.
13. **Goldsmith, R. S., Beatler, F. C., Rosch, P. J., Maroney, W. H.,** and **Herdoon, E. J.:** J. Clin. Endocrinol. and Metab., **18,** 323, 1958.
14. **Gudner, L. I., Talbot, N. B., Cook, C. D., Berman, H.,** and **Uribe, C. R.:** J. Lab. & Clin. Med., **35,** 592, 1950.
15. **Hellem, A. G.:** Acta med. Scandinav., **155,** 271, 1956.
16. **Hewlett, J. S., McCullagh, E. P., Farrell, G. L., Dustan, H. P., Poutasse, E. F.,** and **Proudfit, W. L.:** J. Am. Med. Assn., **164,** 719, 1957.
17. **Holten, C.,** and **Petersen, V. P.:** Lancet, **2,** 918, 1956.
18. **Hudson, B., Barnett, A. J.,** and **Bornstein, J.:** Australian Ann. Med., **6,** 325, 1957.
19. **Kretchmer, N., Dickinson, A.,** and **Karl, R.:** A.M.A. Am. J. Dis. Child., **94,** 452, 1957
20. **Mader, I. J.,** and **Iseri, L. T.:** Am. J. Med., **19,** 876, 1955.

21. **Mellinger, R., Thesian, B., Kline, I. T., Ditzler, J.,** and **Smith, R.:** Henry Ford Med. Bull., **6**, 1, 1958.
22. **Milne, M. D., Meuhreke, R. C.,** and **Avid, I.:** Quart. J. Med., **26**, 317, 1957.
23. **Nicholson, T. F.:** Fed. Proc., **18**, 449, 1959.
24. **Ortuzar, R., Thomsen, D.,** and **Gonzalez, J.:** Rev. Med. de Chile, **86**, 864, 1958.
25. **Scarce, R. C.,** and **Whitstone, W. E.:** A.M.A. Arch. Int. Med., **102**, 1311, 1958.
26. **Sayer, E. G.,** and **Eyre, K. E.:** Lancet, **2**, 63, 1955.
27. **Skavse, B., Moller, F., Gudell, K., Johanson, S.,** and **Wulff, H. B.:** Acta med. Scandinav., **158**, 181, 1957.
28. **von Buchem, F. S. P., Doorenbos, H.,** and **Elings, H. S.:** Lancet, **2**, 335, 1956.

SUMMARIO IN INTERLINGUA

Aldosteronismo Primari: Observationes in Duo Casos

Esseva incontrate, in le curso del passate anno, 2 patientes con primari aldosteronismo causate per aldosteronoma. Le manifestationes clinic esseva multo dissimile in le 2 casos e non coincideva con le syndrome como illo es describite in multes del reportos in le litteratura. Le prime caso esseva illo de un negra de 45 annos de etate qui habeva essite tractate a un altere hospital pro hypertension durante un periodo de 5 annos. Illa esseva admittite in un stato de collapso del circulation peripheric. Isto habeva essite precedite per un acute episodio de diarrhea. Hypokaliemia, initialmente interpretate como effecto del diarrhea, se provava resistente al therapia de administrationes de kalium durante un periodo de plure septimanas. Iste patiente non admitteva ulle symptomas de debilitate, de paralyse, o de tetania ante su hospitalisation. Le secunde patiente esseva un femina de racia blanc de 50 annos de etate qui esseva admittite al hospital pro le tractamento de menorrhagia. Hypertension e edema habeva essite sub tractamento durante 4 annos. In duo occasiones, le administration de diureticos habeva resultate in breve episodios de extreme grados de debilitate muscular. In ambe casos, le insufflation retroperitonee de CO_2 demonstrava un allargamento del glandula sinistro-adrenal. Specimens de urina de 24 horas revelava nivellos elevate de aldosterona (80 e 24 μg, respectivemente), con normal excretion de 17-cetosteroide e 11-oxysteroide. Le ablation chirurgic del adrenales demonstrava adenomas quasi identic in le duo casos. Grande quantitates de sales de kalium esseva requirite pro mantener normal nivellos seral de iste electrolyto durante le periodo operatori. Post le operation, le tension del sanguine descendeva usque a nivellos de choc in un del casos e usque al nivello normal in le altere. In ambe casos il occurreva un periodo transiente de hypertension durante le administration de cortisona post le operation. Le anormalitate del tolerantia pro glucosa reverteva al stato normal post le recuperation.

Le disveloppamento de insufficientia adrenal in un del casos esseva probabilemente le effecto del trauma de un insuccessose tentativa de effectuar un biopsia renal un anno post le ablation del glandula adrenal al altere latere. Therapia substitutive succedeva a maestrar iste complication.

INCREASED ALDOSTERONE EXCRETION DURING CHRONIC SODIUM DEPRIVATION IN TWO MALE SUBJECTS*

By Richard E. Bailey, M.D.†
USPHS TRAINEE IN DIABETES AND METABOLIC DISEASE

AND

Kathleen E. Roberts, M.D.
ASSISTANT CLINICAL PROFESSOR OF MEDICINE

(From the Department of Medicine, Stanford University School of Medicine, and the U.S. Public Health Service Hospital, San Francisco, California)

Early work suggested that sodium deprivation causes the adrenals to secrete an electrolyte-active hormone (Deane[5]). In humans, this hormone was later identified as aldosterone, both in urine (Axelrad *et al.*[1], Duncan, Liddle and Bartter[7], Luetscher and Axelrad[9], Ulick, Laragh and Lieberman[11]) and blood (Ayres *et al.*[2]). The effects of long-term severe sodium restriction have not been so clearly studied. Therefore, 2 patients who had been on a low-salt diet for several months were studied to determine their urinary output of adrenal steroids. Both patients had increased amounts of aldosterone in the urine; as well as urinary conservation of sodium.

Methods. The 2 patients reported here were hospitalized and maintained on a low sodium intake (approximately 6 mEq. per day). The feedings were given by nasogastric tube and supplemented with adequate vitamins and potassium. One patient (M.M.) had arteriosclerosis and senile depressive psychosis, and the other patient (M.R.) had a cerebrovascular accident. The period of sodium restriction in the first patient (M.M.) was for 11 months, and in the second patient (M.R.) was for 15 months. Twenty-four-hour urines were collected and cooled immediately by standard refrigeration. Aliquots were taken for analysis of creatinine, electrolytes, 17-ketosteroids, and 17-hydroxycorticosteroids. The remainder was frozen at −20° C. for the determination of aldosterone. The 17-ketosteroids and the 17-hydroxycorticosteroids were analyzed by the methods of Drekter *et al.*[6], and Sandberg *et al.*[10]. Aldosterone was extracted (Luetscher and Axelrad[9], extract B), and analyzed by chromatography (Burton, Zaffaroni and Keutmann[3]) and bioassay (Johnson[8]).

Results and Discussion. The pertinent electrolyte findings in the serum are shown in Table 1. Serum sodium was normal in the first patient (M.M.) and low in the second patient (M.R.). In both patients the urinary excretion of sodium was low, whereas potassium excretion was normal.

TABLE 1.—SERUM ELECTROLYTE CONCENTRATIONS

Patient # *(Initials)*	*mEq./L.* *Na*	*K*	*CO_2*	*Cl*
#1 (M.M.)	137	4.6	25	90
#2 (M.R.)	114	5.5	26	70

The excretion of adrenal steroids is shown in Table 2. As shown, the aldosterone excretion was increased in both patients, one of the patients having

*This project was supported by a research grant (A-630) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

†Present Address: Veterans Administration Hospital, San Francisco, California.

an aldosterone excretion significantly higher than reported in acute sodium deprivation. The other patient had an aldosterone excretion comparable to that seen in acute sodium deprivation in this laboratory (Axelrad *et al.*[1], Luetscher and Axelrad[9]).

Both 17-ketosteroids and 17-hydroxycorticosteroids were considered to be compatible with the age and general debility of the patients studied. In the second patient (M.R.), the low serum sodium and chloride may be due to gastrointestinal loss from occasional diarrhea.

The results indicated that aldosterone excretion may have been elevated because of sodium restriction. These high aldosterone values seem to be at variance with a recent report (Crabbé, Ross and Thorn[4]) in which aldosterone excretion tended to decline after a maximum had been reached. In our patients, however, it cannot be ruled out that the aldosterone excretion was increased by other factors, such as arteriosclerosis and chronic illness. Neither of the patients had edema, significant impairment of hepatic or renal function, nor any disease known to be associated with increased aldosterone excretion.

Summary. The urinary excretion of adrenal steroids, sodium, and potassium was studied in 2 chronically ill patients. One had been on a low sodium intake (approximately 6 mEq. per day) for 11, and the other for 15 months. Aldosterone excretion measured by bioassay was increased in both patients. In one patient, aldosterone excretion was higher than reported in acute sodium deprivation by this method, and in the other, the value was comparable to that seen in acute sodium deprivation in this laboratory. Excretion of 17-ketosteroids and 17-hydroxycorticosteroids was compatible with the age and debility of the subjects studied. In both patients the urinary intake and excretion of sodium were low, whereas potassium intake and excretion were normal.

The results suggest that aldosterone excretion may have been elevated because of chronic sodium restriction, but do not rule out the presence of other factors which might elevate aldosterone excretion.

TABLE 2.—URINE STEROID AND ELECTROLYTE EXCRETION

Patient # (Initials) (Age)	*17-keto-* steroids*	*17-Hydroxy-† corticosteroids*	*Aldosterone‡*	*Sodium*	*Potassium*
	mg./24 hrs.		*μg./24 hrs.*	*mEq./24 hrs.*	
#1 (M.M.) (Age 79)	7.0	5.9	26.2	8.4	53
#2 (M.R.) (Age 52)	8.0	9.2	12.9	5.6	40

*Normal range in adult males is 10 to 22 mg. per 24 hours.
†Normal range in adult males is 6 to 12 mg. per 24 hours.
‡The range of aldosterone excretion in normal adult subjects on unrestricted diets in this laboratory is 1 to 3 μg. per 24 hours.

REFERENCES

1. **Axelrad, B. J., Cates, J. E., Johnson, B. B., and Luetscher, J. A., Jr.:** Brit. Med. J., **1**, 196, 1955.

2. **Ayres, P. J., Garrod, O., Tait, S. A. S., Tait, J. F., Walker, G.,** and **Pearlman, W. H.:** Ciba Foundation Colloq. Endocrinology, **11,** 309, 1957.
3. **Burton, R. B., Zaffaroni, A.,** and **Keutmann, E. H.:** J. Biol. Chem., **188,** 763, 1951.
4. **Crabbé, J., Ross, E. J.,** and **Thorn, G. W.:** J. Clin. Endocrinol. & Metab., **18,** 1159, 1958.
5. **Deane, H. W.:** Pituitary-Adrenal Function. Washington: American Association for the Advancement of Science, p. 31, 1951.
6. **Drekter, I. J., Pearson, S., Bartczak, E.,** and **McGavack, T. H.:** J. Clin. Endocrinol., **7,** 795, 1947.
7. **Duncan, L. E., Jr., Liddle, G. W.,** and **Bartter, F. C.:** J. Clin. Invest., **35,** 1299, 1956.
8. **Johnson, B. B.:** Endocrinology, **54,** 196, 1954.
9. **Luetscher, J. A., Jr.,** and **Axelrad, B. J.:** Proc. Soc. Exper. Biol. & Med., **87,** 650, 1954.
10. **Sandberg, A. A., Nelson, D. H., Glenn, E. M., Tyler, F. H.,** and **Samuels, L. T.:** J. Clin. Endocrinol. & Metab., **13,** 1445, 1953.
11. **Ulick, S., Laragh, J. H.,** and **Lieberman, S.:** Tr. Assn. Am. Phys., **71,** 225, 1958.

SUMMARIO IN INTERLINGUA

Augmento del Excretion de Aldosterona, Notate in Duo Subjectos Mascule in Chronic Deprivation de Natrium

Le excretion urinari de steroides adrenal, de natrium, e de kalium esseva studiate in 2 chronicamente malade patientes. Lor regime habeva includite le restriction del ingestion diurne de natrium a circa 6 mEq durante 11 e 15 menses, respectivemente. Le excretion de aldosterona, mesurate per bio-essayage, esseva elevate in ambe casos. In un del casos, le excretion de aldosterona esseva plus alte que le valores reportate pro acute deprivation de natrium super le base de studios usante le mesme methodo, e in le altere le valor esseva comparabile al constatationes facite in iste laboratorio in acute deprivation de natrium. Le excretion de 17-cetosteroide e de 17-hydroxycorticosteroide esseva compatibile con le etate e le debilitate del subjectos studiate. In ambe casos, le acceptation e le excretion urinari de natrium esseva basse, illos de kalium esseva normal.

Le resultatos suggere que le excretion de aldosterona esseva possibilemente augmentate in consequentia del chronic restriction de natrium, sed il remane le possibilitate que altere factores esseva presente in elevar le excretion de aldosterona.

THE TREATMENT OF RESPIRATORY ACIDOSIS WITH THAM*

By Geoffrey L. Brinkman, M.D.
ASSOCIATE PHYSICIAN, PULMONARY DIVISION

Donald G. Remp, Ph.D.
SENIOR ASSOCIATE, DEPARTMENT OF LABORATORIES

E. Osborne Coates, Jr., M.D.
PHYSICIAN-IN-CHARGE, PULMONARY DIVISION

E. McCall Priest, M.D.
ASSOCIATE PHYSICIAN, CARDIOLOGY DIVISION

(From the Henry Ford Hospital, Detroit, Michigan)

Respiratory acidosis is the result of alveolar hypoventilation, and all present methods of treatment are directed at improving this aspect of pulmonary function. If alveolar ventilation cannot be improved, no other effective therapy has been available. Attempts have been made to stimulate respiration by the use of oral or intravenous sodium salicylate but the results are equivocal (Wégria *et al.*[11]), and as oxygen consumption is increased at the same time, the end result may not be beneficial (Tenney and Miller[10]). Similarly, the use of a carbonic anhydrase inhibitor has not been particularly effective in the treatment of respiratory acidosis (Galdston[2]).

Recently Nahas[4] has reported a study in dogs employing Trishydroxymethylaminomethane†, an organic buffer, for the treatment of respiratory acidosis. Administration of 100% oxygen to a normal animal rendered artificially apneic, results in the maintenance of the oxygen saturation at about 50%, but the carbon dioxide tension rises to very high levels. Within an hour 40% of these animals die with a carbon dioxide tension of over 300 mm. Hg. If, however, they are given an infusion of THAM, the arterial pH and carbon dioxide tension can be maintained at normal levels and the animals will subsequently make a complete recovery.

We, therefore, decided to study the effects of this buffer in patients with respiratory acidosis.

Method. Four male patients with respiratory acidosis whose ages ranged from 48 to 61 years were selected for this initial study. Three of these patients had severe diffuse obstructive emphysema with arterial oxygen unsaturation and carbon dioxide retention. The fourth patient had carcinoma of the lung with hypoventilation resulting in respiratory acidosis. This patient also had uremia with a serum urea nitrogen of 116 mg. per 100 ml., but the other 3 patients had no evidence of renal insufficiency.

After a light breakfast, a Riley-Cournand needle was inserted in the brachial artery, and a Foley catheter introduced into the bladder. Breathing room air, the subject was then connected to a Tissot 300 liter spirometer and the expiratory gases collected over a 3-minute period, during which time a specimen of arterial blood and urine was obtained. Following this, 20 gm. of THAM dissolved in 300 ml. of 3.3% glucose was given intravenously at such a rate as to allow the infusion to be completed within a 40-minute period. At 20 and 40 minutes after the start of the THAM infusion, arte-

*Trishydroxymethylaminomethane, which is also sometimes known as Tris.

†Trishydroxymethylaminomethane hereafter will be referred to as THAM in this paper.

rial blood and urine specimens were obtained and the expired gases collected for 3 minutes. Further blood and urine specimens were obtained and gas collection made at 70 minutes. A final urine specimen was obtained 100 minutes after the start of the THAM infusion.

Arterial carbon dioxide (PCO_2) and oxygen tensions (PO_2) were determined by the method of Riley, Proemmel and Franke[8], as modified by Brinkman, *et al.*[1]. The pH was measured at body heat on a Cambridge pH meter. The minute ventilation was calculated from the 3-minute collection of expired gases and corrected to standard temperature and pressure. The pH of the urine was measured by use of a glass electrode, and the urinary bicarbonate content determined with the Van Slyke apparatus (Peters and Van Slyke[7]).

Results. The results of administration of THAM on the ventilation, arterial blood, and urine will be considered separately, but are summarized in Table 1.

VENTILATION. Measurements of minute ventilation showed a consistent reduction during the THAM injection. The only exception, as seen in Fig. 1, was in patient W.B., who soon after

TABLE 1.—THE ARTERIAL BLOOD MINUTE VENTILATION AND URINARY FINDINGS ON THE PATIENTS STUDIED

I.

	Blood			$\dot{V}$	Urine	
Spec.	PO_2	pH	PCO_2	L./min.	pH	HCO^-_3
1	49	7.39	70.5	8	6.8	5.4
2	33	7.44	63	7.7	7.4	30.4
3	30	7.45	61	6.3	7.6	78.0
4	39	7.41	70	7.4	7.7	101.0

II.

	Blood			$\dot{V}$	Urine	
Spec.	PO_2	pH	PCO_2	L./min.	pH	HCO^-_3
1	49.5	7.37	61	9.5	5.7	Tr
2	38	7.39	57.5	8.45	7.4	36
3	39.5	7.39	63	8.10	7.7	71
4	46	7.39	65	8.45	7.7	86

III.

	Blood			$\dot{V}$	Urine	
Spec.	PO_2	pH	PCO_2	L./min.	pH	HCO^-_3
1	69.5	7.34	55	6.3	4.85	Tr
2	57	7.41	47	3.15	7.5	9.7
3	44	7.41	55.5	4.2	7.8	60.2
4	60	7.36	60	5.6	7.8	67.6

IV.

	Blood			$\dot{V}$	Urine	
Spec.	PO_2	pH	PCO_2	L./min.	pH	HCO^-_3
1	55.5	7.40	45	11.3	5.3	Tr
2	35	7.45	46	8.4	5.3	Tr
3	—	7.5	47	10.5	7.0	13.1
4	52.5	7.44	55	9.45	7.7	38.2

Specimen 1. At rest
Specimen 2. 20 minutes after starting THAM
Specimen 3. 40 minutes after starting THAM
Specimen 4. 30 minutes after stopping THAM

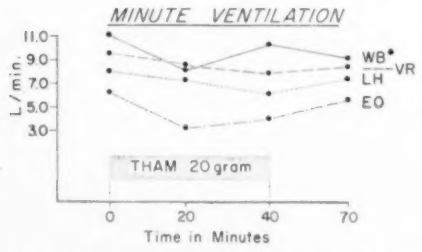

Fig. 1.—Shows the effects of the THAM infusion on minute ventilation.
*This subject had Cheynes-Stokes respiration from the 20- through 70-minute period of observation.

the injection of THAM developed Cheyne-Stokes respiration and continued this abnormal respiration for the following one and a half hours. Because of the Cheyne-Stokes breathing, the calculation of the minute volume is probably inaccurate, which may account for the rise in the minute ventilation at the 40-minute period.

ARTERIAL BLOOD CHANGES. *pH.* During administration of THAM, there was a consistent rise in the pH in all 4 subjects (see Fig. 2). The greatest rise occurred in W.B. who was uremic. This was probably due to the delayed excretion of bicarbonate because of renal insufficiency, as a result of which the alkali reserve increased to a greater extent than in the other 3 individuals.

Carbon Dioxide Tension. This was initially raised in all 4 patients, ranging from 45 to 70.5 mm. mercury. Following administration of THAM, in 3 subjects there was no significant change in the PCO_2. In the fourth individual (L.H.), the initial PCO_2 of 70.5 mm. mercury fell during the infusion to 61 mm. mercury despite a 20% reduction in minute ventilation.

Oxygen Tension. While all these patients had decreased oxygen tension (50, 56, 70, 49 mm. Hg) at the start of the experiment, the PO_2 decreased further in amount from 11 to 25 mm. mercury during the course of the THAM infusion. This change was probably the result of the decrease in minute ventilation and not related directly to the THAM. The shift to the left in the oxyhemoglobin curve due to the higher pH would result in some fall in PO_2, but not sufficient to account for the change produced in these individuals.

URINE. The most marked and consistent changes were in the urine where a similar pattern was followed in each individual (Fig. 3). The urinary pH rose within 20 minutes of the start of the infusion of THAM with the exception of the uremic patient (W.B.) in whom the rise in the pH was delayed until the 40-minute specimen. There was also a consistent and marked rise in the urinary bicarbonate in all 4 subjects. In the pre-infusion specimen and in the 20-minute specimen, there was usually just a trace of bicarbonate

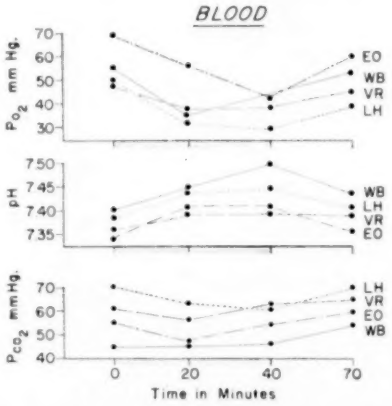

Fig. 2.—Demonstrates the changes in arterial blood following THAM intravenously given over a 40-minute period as indicated by the shaded area.

which rose to higher levels in the next 2 specimens, but was beginning to fall after 100 minutes.

Discussion. The usual therapeutic agents employed to counteract acidosis are the salts of weak organic acids, but THAM, in contrast, is a weak organic base which at a pH of 7.4 is 80% dissociated (Gomoni[3]).

From the above study, it is evident that THAM is an effective buffering agent which is capable of raising the arterial pH. Simultaneously the minute ventilation is appreciably reduced despite the PCO_2 being maintained at approximately the same level throughout the experiment. This reduction in minute ventilation appears to be closely related to the rise in pH, indicating that the respiratory center is responding to a change in the arterial pH independently of any change in PCO_2.

In these 4 individuals the respiratory minute volume was reduced, which would result in less excretion of carbon dioxide from the lungs. Despite this, the PCO_2 remained relatively unchanged, which is probably due to increased urinary excretion of bicarbonate. This was confirmed by Nahas[5] who showed that in dogs with apneic oxygenation, the maintenance of a normal PCO_2 is accounted for by the excretion of the excess carbon dioxide as urinary bicarbonate.

Because of the beneficial effect on respiratory acidosis obtained in this study, we have used the buffer therapeutically in 2 patients.

Case Reports. CASE 1. (L.P.) The first patient was a 30-year-old woman who following cardiac surgery developed severe respiratory acidosis. She did not respond to the usual methods of therapy, and as the situation was desperate, she was given 120 gm. of THAM in water by gastric tube over a 24-hour period. She developed fairly severe diarrhea, and as the acidosis was relieved, also developed tetany, which was controlled with calcium gluconate given intravenously. Her arterial pH was raised from 7.1 to 7.45 following THAM administration, and she subsequently had no further respiratory acidosis. However, she died of other complications a few days later. At necropsy there were no ill effects attributable to THAM administration.

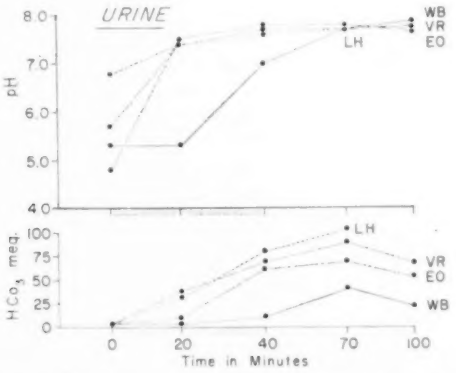

Fig. 3.—The urinary changes resulting from THAM infusion, the duration of which is again indicated by the shaded area.

CASE 2. (H.S.) (See Table 2) A 40-year-old white man who 20 years previously had had a 9-rib thoracoplasty on the right side, was admitted with an extensive left-sided pneumonia. At the time of admission he was not thought to be acutely ill. However, over the next 12 hours, he became unconscious with slow gasping respirations. Tracheotomy was done without any appreciable improvement. Arterial blood studies done at the

time he was receiving 100% oxygen by a Bennett IPPB machine connected to the tracheostomy, showed that his oxygen saturation was 97%, but the carbon dioxide tension was 160 mm. of mercury and the pH was 6.95. He was put in a Drinker respirator but after 3 hours there was no improvement in his condition. A repeat arterial blood study at this time showed no change from the previous study. Over the next hour and a half he was given 30 gm. of THAM as a 10% solution in water through a gastric tube. Two hours after starting the infusion, he regained consciousness. Five minutes later he developed tetany which responded to intravenous calcium gluconate. He was still receiving oxygen through the tracheostomy, but now his arterial blood showed a saturation of 92%, and a CO_2 tension of 89 mm. of mercury, with a pH of 7.2. He continued in the respirator, and 5 hours later was given a further 10 gm. of THAM through the gastric tube. The last arterial blood was obtained 12 hours after he became conscious, at which time he was out of the respirator and the oxygen had been discontinued for 15 minutes. The oxygen saturation was now 49%, the PCO_2 68 mm., and the pH was 7.29. He was normally responsive and apparently had no mental changes as a result of his profound narcosis. He was given oxygen and appeared to be doing well, but respiration suddenly ceased and he died. At necropsy he was found to have a cerebellar tonsillar pressure cone. The bronchial tree was clear, and death was attributed to central respiratory arrest.

TABLE 2.—THE ARTERIAL BLOOD STUDIES ON CASE 2 (H.S.)

Specimen	*pH*	*PCO_2*	*Cco_2*	*So_2*
1	6.95	160	38.80	96.6
2	6.94	160	38.10	86.7
3	7.20	89	36.50	91.5
4	7.29	68	33.70	49.70

Specimen 1. Tracheotomy plus 100% O_2
Specimen 2. Tracheotomy plus 100% O_2 plus Drinker Respirator
Specimen 3. As above, after 30 gm. of THAM
Specimen 4. 12 hours later, out of respirator, no O_2 for 15 minutes

Results of this preliminary study indicate that THAM is well tolerated, and even in the patient (W.B.) with uremia, there was no deterioration in renal function following the THAM infusion. There has been no thrombophlebitis at the site of the injection but in one patient some of the buffer extravasated outside of the vein, with resultant local sloughing of the overlying skin. In both patients in whom this drug was given orally, there has been some diarrhea. Also, in these 2 patients tetany developed as the acidosis was relieved, but this was easily controlled by intravenous calcium gluconate.

Although we have not experienced any ill effects following administration of THAM, significant hypoglycemia has been reported by Tarail and Bennett[9]. Twenty-seven to 76 gm. of THAM given intravenously over a 49- to 64-minute interval resulted in a fall in the blood sugar of up to 37 mg. per 100 ml., which effect disappeared within an hour. Nahas, Dos and Ligau[6] have also reported hypoglycemia following a similar intravenous dosage of THAM. We have not given more than 20 gm. intravenously at any one time, which probably accounts for the fact that we have not observed side effects indicative of hypoglycemia.

Summary. The effect of Trishydroxymethylaminomethane (THAM) on 4 individuals with respiratory acidosis is recorded. There was a consistent rise in the arterial blood pH, a reduction in minute ventilation, and a considerable increase in urinary pH, and urinary excretion of bicarbonate. A brief report on the 2 patients in whom this buffer has been used therapeutically is included.

REFERENCES

1. **Brinkman, G. L., Johns, C. J., Donoso, H.,** and **Riley, R. L.:** J. Appl. Physiol., **7**, 340, 1954.

2. **Galdston, M.:** Am. J. Med., **19,** 516, 1955.
3. **Gomoni, G.:** Proc. Soc. Exper. Biol. & Med., **62,** 33, 1946.
4. **Nahas, G. G.:** Science, **129,** 782, 1959.
5. Idem: Personal communication.
6. **Nahas, G. G., Dos, J. J.,** and **Ligau, J. G.:** Reported at Annual Meeting of the Eastern Section of American Federation for Clinical Research, December, 1959.
7. **Peters, J. P.,** and **Van Slyke, D. D.:** Quantitative Clinical Chemistry. Baltimore: The Williams & Wilkins Co., 1931.
8. **Riley, R. L., Proemmel, D. P.,** and **Franke, R. E.:** J. Biol. Chem., **161,** 621, 1945.
9. **Tarail, R.,** and **Bennett, T. E.:** Proc. Soc. Exper. Biol. & Med., **102,** 208, 1959.
10. **Tenney, S. M.,** and **Miller, R. M.:** Am. J. Med., **19,** 498, 1955.
11. **Wégria, R., Capeci, N., Kiss, G., Glaviano, V. V., Keating, J. H.,** and **Hilton, J. G.:** Ibid., **19,** 509, 1955.

SUMMARIO IN INTERLINGUA

Le Tractamento de Acidosis Respiratori con Trishydroxymethylaminomethano

Es reportate le effecto de trishydroxymethylaminomethano (THAM) in 4 subjectos con acidosis respiratori. Occurreva uniformemente un augmento del pH de sanguine arterial, un reduction del ventilation per minuta, e augmentos considerabile del pH urinari e del excretion urinari de bicarbonato. Es includite un breve reporto de 2 casos in que le tampon THAM esseva usate therapeuticamente.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

ROGER W. REED, M.A., M.D., C.M.
PROFESSOR OF BACTERIOLOGY AND IMMUNOLOGY, McGILL UNIVERSITY

AND

GARDNER C. McMILLAN, M.D., C.M., M.Sc., PH.D.
STRATHCOMA PROFESSOR OF PATHOLOGY, McGILL UNIVERSITY
MONTREAL, CANADA

BACTERIAL INFECTIONS OF ANIMALS TRANSMISSIBLE TO MAN

BY L. W. MACPHERSON, PH.D. (EDIN.), M.R.C.V.S., D.V.S.M.
ASSOCIATE PROFESSOR OF MICROBIOLOGY, SCHOOL OF HYGIENE,
UNIVERSITY OF TORONTO, TORONTO, CANADA

THE transmission of bacterial and other infections from animals to man has been recognized since the earliest times. The biblical admonitions of Moses to the children of Israel, expounded in Deuteronomy[40], are probably based on the necessity of preventing transmission of animal infections to man, and have been preserved in Jewish ritual slaughter of livestock to this day.

However, the widespread recognition of the many infections of animals transmissible to man has been of comparatively recent date, and the measures to control this hazard to public health and indeed the very recognition of some of the diseases transmissible to man, are only now being presented.

Broadly speaking one can divide the bacterial infections of animals transmissible to man into two groups:

(a) *Infections of considerable public health significance*

1. Anthrax
2. Brucellosis
3. Erysipeloid
4. Leptospirosis
5. Plague
6. Rat-bite fever
7. Salmonellosis
8. Tuberculosis
9. Tularemia

(b) *Recently recognized infections whose public health significance is difficult to assess*

1. Listeriosis
2. *Pasteurella multocida* infections
3. Vibriosis

ANTHRAX. Anthrax is a disease primarily of herbivora and secondarily of man and other animals. Its origin is shrouded in the mists of antiquity and it is believed by many that one of the scourges which beset the Egyptians during the Israelites' captivity may have been this disease[41]. Certainly the ancient Greek writers have described devastating epizootics in animals and associated disease in man which many consider to have been anthrax[101]. For centuries the pathology of anthrax was not understood, but in 1849 Pollender[84] observed that the blood of anthrax animals contained numerous rod-shaped bodies, which he postulated had some causal connection with the disease. In 1863 Davaine[16,17] announced that these were bacteria and that they were the causal agents of anthrax. The classical researches of Koch in 1876[57] and Pasteur in 1880[85] were most timely. They clarified the position regarding the etiology of anthrax, and evolved a vaccine against it at a time when some 25 to 50% of the sheep flocks of Europe were dying of this disease, and when the entire agricultural economy was facing disaster.

The anthrax organism was first fully investigated by Robert Koch[58], who observed the division of the organism and also spore formation. He isolated the organism in pure culture, and by inoculating animals reproduced the disease. It is one of the largest organisms, measuring approximately 1 to 1.3 by 3.0 to 10.0 microns[6], and is non-motile, Gram-positive, spore-forming, and capsulated. The spore form is extremely resistant to heat, and Murray[76] has demonstrated the thermal death point at 135° C. for 10 minutes (dry heat), or 105° C. for 10 minutes (moist heat). Smith has shown that anthrax spores were capable of germinating after 22 years[35]. Lye, 5%, is probably the most satisfactory chemical disinfectant, being effective against spores in 24 hours. The vegetative form of the organism is readily destroyed by chemical disinfection, heat, or drying[67], a factor which is extremely important in the epidemiology of this disease.

Geographically, anthrax is worldwide in distribution but has a comparatively low incidence today in countries where restrictive measures have been instituted. Conversely, in most countries where animal control measures are lacking, the incidence of anthrax continues to be high[61]. The incidence of human anthrax is said to be low as compared with the other zoonoses, but the WHO/FAO Expert Committee on the zoonoses has indicated an incidence of 9,000 cases annually. Most of these occur in rural districts, although industrial infections may be frequent. Due to under-reporting, it is suggested by this committee that the actual incidence may be up to 90,000[113].

The spread and maintenance of anthrax infection in certain regions is related to the long survival time of the spore forms. Pastures in which infected cattle have roamed may remain contaminated for many years, while industrial effluents, for example, tannery wastes, also serve as a potential source of pasture and water contamination[24]. The use of artificial feeding stuffs, for example, bone meal, are also a potential source of infection for cattle[20]. In cattle and sheep, the disease usually takes the acute form, and is septicemic in type with excitement, respiratory and cardiac distress, convulsions and death the usual sequence of events. Hemorrhagic discharges from the natural orifices of the cadaver are frequently observed and these are heavily contaminated with anthrax organisms which on exposure to air tend to spore rapidly[32]. The blood of such cadavers is teeming with the vegetative forms.

Human anthrax infection is usually acquired through abrasion or other small wound of the skin. Less frequently, infection of the lungs may occur through inhalation of spores, as in Woolsorter's disease, and finally and most infrequently, by ingestion. The persons most frequently affected are those having contact with animals or their products, such as butchers, stockmen, and industrial workers in the hide, hair or meat industries. Heeren[39] has suggested that biting insects are involved in the transmission of the disease. Certainly, contact with the animal may be remote, as is the case when an individual is infected while shaving as a result of anthrax spores being present on a shaving brush.

(a) *Cutaneous Anthrax (Malignant pustule)*[80]. The incubation time in these cases is from 1 to 3 days. At the site of inoculation, usually on an exposed surface, there develop itching, uneasiness and the gradual development of a small papule which later becomes vesicular. Inflammatory induration develops around this and within 36 hours there develops at the site of inoculation a dark brown eschar at a little distance from which there may be a series of small vesicles. There is considerable redness at the site and the inflammation spreads along lymphatics to the local lymph nodes. The fever rises rapidly in the early stages and falls abruptly after several days. The mortality rate prior to the advent of sulfonamides and penicillin was 26.6%[1] but early diagnosis and treatment with penicillin and other antibiotics have reduced the mortality almost to zero[114].

(b) *Pulmonary Anthrax (woolsorter's disease)*. In this form there are no premonitory signs. The patient develops a chill and temperature rises to 102 to 103° F. Breathing is rapid and there is pain in the chest, back and legs. The pulse is feeble and rapid and death may occur within 24 hours with profound collapse.

(c) *Internal Anthrax (intestinal form)*. The symptoms in these cases are those of internal poisoning. The disease may set in with a chill followed by vomiting, diarrhea, moderate fever and pains in the legs and back. In acute cases there are dyspnea, cyanosis, restlessness and convulsions. Hemorrhage may occur from the mucous membranes.

Treatment with penicillin and other wide-spectrum antibiotics has reduced the mortality rate almost to zero. Various vaccines for the use of exposed groups have been suggested[19].

BRUCELLOSIS. Brucellosis is primarily a disease of domestic animals which under special circumstances may be transmitted to man. It is world-wide in distribution but is more prevalent in areas in which extensive cattle, swine, and goat herding is practiced. It causes serious economic loss to the animal industry and extensive morbidity in man thus constituting an important public health problem[15].

Abortion, the outstanding clinical sign of brucellosis in animals, was early recognized as an infectious disease by herdsmen, while in the early part of the 19th century the disease "Mediterranean fever" was observed in man. However the investigation of the animal and human disease entities went their separate ways. In 1886 Bruce[14] isolated one of the causal agents of Mediterranean fever, while in 1895 Bang[4] isolated the causal organism of the animal disease. Zammit's[121] outstanding observation in 1904 of the relationship between the consumption of goat's milk and the incidence of Mediterranean fever opened the way for Evans[26] in 1918 to carry out her classical studies, which linked the various animal Brucella infections to the human disease, undulant fever.

Generally speaking, *Brucella melitensis* is considered to be the agent responsible for bovine and caprine brucellosis, *Brucella abortus* for bovine brucellosis, and *Brucella suis* for porcine brucellosis. Actually, infection of any species of animal by any type of Brucella is frequent, and, one can say in effect that the specific relationship of Brucella types to animals does not exactly correspond[90].

The morphological characteristics of the three species of Brucella are similar, being short ellipsoidal, non-motile, Gram-negative rods about 0.3 to 0.4 micron in length. They can only be differentiated by cultural, biochemical and serological tests[7].

Reasonable estimates of the prevalence of brucellosis are difficult to obtain because in most countries Brucellosis in man or animals is not notifiable. In many countries *Br. abortus* infection of cattle is known to be as high as 30%[99]. Brucellosis is also known to occur extensively in goats, swine and sheep. The figures of human cases notified are very variable, but the Epidemiological and Vital Statistics Reports of the World Health Organization show that while brucellosis is world wide in distribution, the Mediterranean and particularly Italy and Spain still have the highest incidence (4,000 to 10,000 cases annually).

In animals, infection can occur by ingestion, inhalation, or through the skin, conjunctivae, or mucous membranes. The origin of the infective material varies. It can be the aborted fetus and membranes, infected genital discharges, urine, or milk.

Taylor and his co-workers[104] give an interesting breakdown of origins and methods of infection in 466 cases of human infection.

In this series contact infection is apparently 5 times as frequent as ingestion infection, a view which opposes much of the writing in the literature. Renoux[90] suggests that ingestion infection is of major significance in towns and is probably responsible for most cases. Infection by contact on the other hand is more frequent in rural areas and is responsible for the majority of cases there.

It is impossible to give more than a brief summary of the symptomatology of human brucellosis which is very wide and varied. All the symptoms encountered in Brucella infection can be observed in other diseases. However, according to Renoux[90] there are two general forms, namely, a) An acute fever of limited duration followed by apparent recovery. b) Long continued disease with periodic exacerbation, in which the onset can be insidious and followed by a long illness.

There are distinct variations in the virulence of the three organisms for man, *Brucella melitensis* being the most pathogenic, *Brucella suis* less so, and *Brucella abortus* least pathogenic of all. Similarly, man appears to be more readily infected by *Brucella melitensis* and *Brucella suis*, although comparison of the symptoms in these infections shows the same clinical evolution, namely, asthenia, pyrexia, anorexia, and others. Mortality appears to be considerably higher in *Brucella melitensis* infections. The distinctive transient arthritis which occurs in about 40% of cases is most common in *Brucella melitensis* infection.

The complications include peripheral neuritis, orchitis, meningitis, bronchitis, and endocarditis. Women may develop mastitis and pregnant women may abort, although this manifestation is not so frequent as in animals[81].

Diagnosis of the disease in man can be most difficult as there are no pathognomonic signs. However, all fevers of undetermined origin should be suspect. The diagnostic criteria for hu-

man brucellosis have been well presented by Spink *et al.*[98] who have indicated the necessity of isolation of the causal organism, or, failing that, the demonstration of a rising agglutination titer or titer above 1:320 which offers presumptive confirmation of clinical diagnosis.

The specific therapy of the disease dates from 1946[25,89] when streptomycin was introduced, but the relapse rate was not inconsiderable. McCullough[68] suggests the most satisfactory treatment available is a combination of dihydrostreptomycin, chlortetracycline and triple sulfonamide.

In considering prophylactic measures, it must be remembered that the Brucella essentially attack animals. Consequently control of the disease in man is dependent on its control in animals. Methods of eradication or control of brucellosis in animals are usually based on vaccination and serodiagnosis followed by slaughter or segregation of reactors. These various methods are outlined by the FAO/WHO Expert Committee[115].

ERYSIPELOID. Erysipelas is primarily a disease of pigs and secondarily of other animals, birds, and man. In man, it occurs in most instances in the cutaneous form and is known as erysipeloid.

Erysipeloid has been known in many parts of the world and particularly in the pig-raising areas of Europe for many years. Descriptions of the clinical disease in swine appeared early in the literature and in 1873 Baker[3] described the disease in man. The causal organism is *Erysipelothrix insidiosa* in the smooth form. They are 0.2 to 0.4 by 0.5 to 2.5 microns. In rough colonies larger filamentous forms may occur. The organism is Gram-positive, nonmotile, and non-capsulated and grows readily on ordinary media[8].

This disease appears to be worldwide in distribution. It is an occupational disease occurring in butchers, cooks, kitchen workers, fishermen and game handlers[52]. The incidence is mainly sporadic in these groups although epidemics have been reported. Stefansky and Grünfeld[100] in 1930 described an outbreak at Odessa affecting some 200 handlers of fresh water fish. Lawson and Stinnett[60] in 1933 in the U.S.A. described 247 cases among workers in the button industry who were involved in processing animal bone.

Verge in 1933[107] described three forms of the disease, a cutaneous, intestinal, and a generalized form, but in the majority of cases the cutaneous form is by far the commonest. In 100 cases reviewed by Klauder[56] all but 5 had a history of cutaneous injury at which site the infection first appeared.

Klauder[55] states that infection can invariably be traced to contact with animals, fish, or dead matter of plant or animal origin. The organism gains access through injuries and frequently by bites of animals. Direct transmission from infected swine or animals to man appear to be uncommon, although Morrill[73] has described such transmission to veterinarians.

The incubation time is 1 to 4 days and the first symptom is pain at the site of inoculation, followed by swelling and erythema. The most distinctive feature of the disease, of considerable diagnostic significance, is the purplish-red color of the erythema. The erythema slowly progresses, producing another distinctive feature, a sharply defined, slightly elevated zone, which extends peripherally as the central portion fades away. The involved area is swollen and tense as though fluid had been injected intracutaneously. If the finger is involved the swelling and tenseness make movement difficult. At times vesicles which may be hemorrhagic occur at the site of the erythema.

Another characteristic of the disease is its migratory nature: new purplish-red patches may appear at remote areas. The disease involutes without desquamation[53].

Complications include arthritis particularly of the joints near the involved part; a diffuse and generalized eruption which parallels the mild form of infection in swine; or a septicemia with or without endocarditis. Meningitis[23] and intracranial abscess[105] have also been attributed to this organism.

The clinical signs are so obvious in most cases that laboratory diagnosis is seldom sought. In septicemic cases the causal agent can be isolated from the blood and in the cutaneous form from the local lesion. A feature of this condition is that serological tests based on agglutination of the causal organism are very unreliable and permanent immunity is seldom established[54].

Penicillin therapy is the method of choice and is superior to other forms of antibiotic treatment.

Prophylaxis depends obviously on prevention of contamination in those individuals exposed to this occupational hazard.

LEPTOSPIROSIS. This disease primarily affects rodents, dogs, cattle and swine and secondarily affects man.

Epidemic jaundice was first described by Weil[112] in 1886. In 1916 Inada[44] reported that a spirochete was the causative agent and Noguchi[78] classified the organism and named it *Leptospira icterohaemorrhagiae*.

Subsequent studies by various European, Australian, Japanese, Indonesian and American investigators have identified many immunologically distinct leptospirae as pathogenic for man and a host of other animals[102].

The causal organisms of leptospirosis are the many immunologically distinct leptospires. The leptospirae commonly isolated from North American cases of leptospirosis are *L. icterohaemorrhagiae, L. canicola, L. pomona, L. bataviae and L. autumnalis*[102]. These are finely coiled organisms measuring 6 to 20 microns in length. The spirals measure 0.3 micron in depth and 0.4 to 0.5 in amplitude. In liquid media either one or both ends are bent into a semicircular hook, involving 1/8 to 1/10 of the organism. Spinning movements occur in liquid media and vermiform movements in semi-solid media. In living preparation the organisms are most readily seen with dark-field microscopy and are invisible by light illumination. They stain with difficulty except by Giemsa or silver impregnation methods[119].

Until comparatively recently, leptospirosis was regarded as a rare disease. Now it can be appreciated that the leptospiroses constitute a major problem in animal disease[74]. Human infection, on the other hand, is accidental and represents a dead end in the chain of transmission.

Among animals the most common species affected by leptospirosis are rodents, dogs, cattle, and swine, although recently a considerable number of wild mammals have been shown to be affected. As one might expect from organisms having such a wide host-spectrum many serotypes have been produced, the most important ones as far as North America is concerned having already been referred to by their specific names.

Of primary significance in transmission of leptospiral infection to man are the animals shedding leptospirae in their urine. After either clinical or subclinical infections the organisms become established in the kidney and are eliminated in the urine. Infection of man and other animals results from direct or indirect contact with such urine[33].

After an incubation period of 3 to

9 days, the disease is initiated by a sudden onset, with chills, high fever, gastrointestinal disturbance, including nausea and vomiting, and muscular pains especially in the calf muscles. During this febrile period, which lasts till about the 5th day, spirochetes are present in the blood stream. Diagnosis at this time is extremely important if therapy is to be effective. However, these early symptoms are shared by many diseases and are not striking features likely to suggest the specific infection. Onset may be much more insidious, even with fatal termination. Conjunctivitis is a common finding, and other early symptoms may suggest pneumonia or meningitis.

In the second stage which extends from the 6th to the 13th day, icterus, hemoglobinuria and tissue hemorrhage, which are much more diagnostic, appear. However, by this time tissues have already been severely damaged. Therapy may fail and the patient may die even though fever and other acute symptoms have subsided. Convalescence, with the appearance of demonstrable antibodies in the blood, begins about the 15th day. Relapses are common in the 3rd to 5th week but recovery is usually uncomplicated. Recovery may be slow. It must be emphasized that in atypical cases there is a wide spectrum of symptoms. Iridocyclitis has recently been recognized as a delayed sequel[46].

As in other infectious diseases, patients suffering from leptospirosis may show all or only a few of the clinical features produced by the serotype involved. Alston and Broom[2] have described three degrees of infection, namely,

1. The classical icterohemorrhagic syndrome which is often fatal.
2. A less severe jaundice and nephritis than occurs in type 1, and with meningitis the central feature. This form is rarely fatal.
3. An influenza-like disease with no fatalities, of which the cardinal symptoms are fever, muscular pains, sore throat, but no jaundice or nephritis.

In the non-icteric cases differential diagnosis without laboratory study is obviously impossible.

Laboratory examination rests on the following: a) Demonstration of leptospirae, which is accomplished by examination of blood, urine or ground tissue by dark ground microscopy for the typical leptospirae; by culture of blood, urine or tissue; by guinea pig inoculation; by microscopical examination of tissues (kidney or liver) taken at necropsy and suitably stained. b) Demonstration of antibodies to leptospira, which is accomplished by agglutination test; by agglutination-lysis test; by complement fixation test; by erythrocyte sensitization test.

The most important lesion in leptospiral infection is renal damage, and antibiotic therapy or specific serum therapy is seldom initiated sufficiently early to protect the kidney. Where the illness is of less than 3 days' duration, then penicillin or tetracycline are usually effective.

Serum treatment has been used prior to the development of antibiotics and satisfactory claims made for it[111].

The preventative measures that might be applied to reduce incidence include: destruction of rodents, food protection, control of infection in domestic animals, limitation of bathing in infected areas, hygiene of individuals, immunization of certain occupational groups, and the prophylactic use of antibiotics in exposed individuals.

PLAGUE. Bubonic plague has been responsible for a number of notable pandemics which seem to have a long-term cyclic frequency. The biblical plague of the Philistines of 1320 B.C. is believed to have been plague and the pandemic of 542 A.D. which affected the entire Roman world is

known to have been plague. The "Black Death" of the 14th Century and the Great Plague of London in 1665 are all known to have been epidemics of bubonic plague. More recent pandemics have involved the Asiatic continent between 1896 and 1918 and the disease was first introduced to the Western hemisphere in 1899 and to the United States with the San Francisco outbreak of 1900[63].

The plague bacillus, *Pasteurella pestis,* is a short plump ovoid rod 1.0 by 2.0 microns, which is non-motile, non-sporing and Gram-negative. Stained by appropriate methods it shows the characteristic bipolar staining[9].

Plague is basically a disease of rats and is spread from rat to rat and from rat to man by the bites of fleas particularly the rat flea *Xenopsylla cheopis*[96]. However there are really three planes of infection in this disease, namely sylvatic, domestic and human[18]. Thus in Africa the sylvatic host is mainly represented by the gerbil, while in South America 10 species of rodents including hares and guinea pigs have been found infected. In the United States, marmots, prairie dogs, hares, rabbits and squirrels have all been found infected naturally.

Infection can obviously occur directly from the sylvatic phase to the human phase through bites of infected fleas, but more frequently, and particularly where the disease assumes epidemic proportions, such outbreaks are preceded by epizootics at the domestic plane among the rat population.

Fleas feeding on infected rodents suffering from plague bacteria become carriers by virtue of a "blocking" phenomenon. The proventriculus or forestomach of the flea is blocked by masses of plague bacilli and thus no food can pass into the true stomach. This results in the flea traveling from host to host and biting continuously in attempts to satiate himself.

Four clinical types of plague are described in the literature[82], namely, pestis minor, bubonic plague, pneumonic plague and septicemic plague.

With pestis minor the patient simply has a few days of fever with swelling and possibly suppuration of the lymph nodes of the groin.

Bubonic plague is the commonest variety of clinical infection and has an incubation period of 3 to 4 days. The invasive stage is accompanied by headache, myalgia and depression. There is a steady rise in fever up to the 4th day followed by a drop of 2 to 3 degrees. In at least two-thirds of cases the patient develops the characteristic swelling of the lymph nodes or buboes. Suppuration of the lymph nodes frequently occurs and is a favorable feature. There is marked leukocytosis.

Pneumonic plague begins with fever, shortness of breath, cough and pain in the chest. Impaired resonance of both lung bases develops, sputum becomes blood-stained and fluid, cyanosis develops and death supervenes.

Septicemic plague is the most rapid form and the patient succumbs within 3 to 4 days with a virulent infection and no buboes.

Early in an outbreak the diagnosis can be overlooked. The finding of marked lymph node swellings particularly of the groin should be regarded with suspicion but a definite conclusion depends on bacteriological study. The organisms can be demonstrated in smears from the buboes or in the sputum in pneumonic cases or in the blood in septicemic cases. The organism can be isolated from such materials in culture or in animals, the guinea pig being highly susceptible.

Streptomycin, tetracyclines and chloramphenicol are all effective in treat-

ment. The organism is resistant to penicillin and frequently also to sulfonamides[97].

Control of plague[88] can be effected by sanitary methods against the vectors and the rodent reservoirs; by immunization of the individual[71]; and by strict isolation procedures.

RAT-BITE FEVER. Brown and Nunemaker[13] in their review of rat-bite fever draw attention to the confused state of medical literature on this subject due mainly to the two etiological agents allegedly associated with the disease, namely, *Spirillum minus* and *Streptobacillus moniliformis*.

Rat bites have been appreciated as a cause of disease for centuries and Wilcox[117] in 1839 first described the clinical condition. In 1908 Ogata[79] used the Japanese term "sodoku" to describe the disease and later Japanese workers described spirochete-like organisms in the lesions[31].

In 1914 Schottmüller[93] described the *Streptothrix minus ratti (Streptobacillus moniliformis)* in association with clinical cases of rat-bite fever, and Dolman[21] has recently presented evidence that this is in fact the true etiological agent of rat-bite fever.

As indicated in the introductory paragraph, the etiology is most confused but the recent work by Dolman and his co-workers strongly supports the view that *Streptobacillus moniliformis* is the true causal agent. However, *Streptobacillus moniliformis* is not allocated to a definite genus in Bergey's seventh edition. The organism is a Gram-negative, non-motile rod 2 to 5 by 0.1 to 0.4 micron. It is extremely pleomorphic, and under favorable conditions may grow in long filaments. It may not grow satisfactorily on primary isolation[45].

This disease is probably world-wide in distribution and certainly reports from most parts of the world have occurred. The rat appears to be the true reservoir of infection although Brown and Nunemaker[13] in their review have incriminated other rodents and animals predatory on rodents as sources of infection for man. Strangeways[103] has shown that approximately 50% of wild rats harbor the causal organism. The transmission to man is normally by the bite of a rodent or predator.

In addition, milk-borne transmission has occurred. This was studied by Place[87] in Haverhill, Massachusetts, and it was suggested that the milk was contaminated by rats. Some 86 clinical cases occurred in this outbreak.

The incubation period following the exposure is from 2 to 15 days tending to be longer in the cases following bite than in milk-borne infection, and the disease is abrupt in onset being characterized by fever, nausea, vomiting, and headache. A skin rash occurs fairly constantly and has been variously described as rubellaform, morbilliform, or maculo-papular, some rashes being petechial and purpuric. There is a high incidence of joint involvement associated with this condition, the severity and location of the arthritis, varying from case to case. In most cases there is a series of several paroxysms of 3-day persistence of fever, followed by 5 to 6 day remissions, the symptoms recurring with each febrile period. The mortality rate is low, but complications have included generalized adenitis, conjunctivitis photophobia, and ulcerative endocarditis.

Laboratory diagnosis rests on the isolation of the causal organism, *Streptobacillus moniliformis*. This can be effected by blood culture, the medium containing 20 to 30% serum or ascitic fluid[6]. Patients may yield positive blood cultures for many weeks following exposure.

Streptobacillus moniliformis is sensi-

tive to penicillin and streptomycin but resistant to sulfonamides. In experimental infections in animals streptomycin has proved the most efficacious of these two antibiotics[62].

From the epidemiological pattern it is shown that control rests on the control of the rat population and the efficient pasteurization of milk.

SALMONELLOSIS. Food poisoning has been recognized since the dawn of history but the relationship of the Salmonella to food poisoning was first recognized by Gartner[34] in 1888 when he reported the illness of 57 persons following consumption of the flesh of a cow slaughtered on account of sickness. Gartner isolated the causal organism *Salmonella enteritidis* from the meat and from the organs of one patient who died of the disease.

Subsequently over 150 types of Salmonella organisms have been reported in food-poisoning cases. The Salmonella are Gram-negative, nonsporing, motile rods which do not ferment lactose. They are morphologically identical but can be differentiated by serological tests.

The primary hosts of most Salmonella types are animals, and the domestic fowl is probably the main reservoir as far as human infections are concerned[5]. Eggs and particularly imported dried egg proved a potent source of human infection in the United Kingdom in World War II[70]. The Medical Research Council reported the introduction of 33 new types of Salmonella by this route and showed a greatly increased incidence of food poisoning in the period 1942 to 1945.

In addition to fowls, rodents, swine, cattle, sheep, horses, dogs, and cats, may harbor Salmonella and are potential sources of infection to man. The rodents frequently contaminate human food with their infected excreta, while the meat-producing animals may be a source of infection to man through the consumption of undercooked meat products.

The incubation period is usually less than 24 hours, although occasionally it may be 3 to 4 days. The onset is sudden with a chill followed by fever or the temperature may be subnormal. Vomiting, abdominal pains, and frequent, offensive stools, sometimes bloody, follow, frequently with severe muscular pain and marked collapse. Skin reactions are not uncommon[83].

Diagnosis is usually made from the history and clinical picture but laboratory examination of the stool and isolation and identification of the etiological agent is necessary to confirm the diagnosis.

Treatment is usually physiologic. In most cases the course of the disease is short but the fluid and electrolyte balance may be disturbed and should be restored. Penicillin and sulfonamides are ineffective, while streptomycin only reduces the number of organisms temporarily. Recent work indicates that chloramphenicol and tetracyclines are effective in treatment[22,94].

The control of outbreaks of food-poisoning due to Salmonella infection is concisely dealt with by the WHO/FAO Expert Committee[48], who advise, reporting of cases, education of food handlers, pasteurization of milk, refrigeration of foods, hygienic production and storage of eggs, sterilization of food liable to contamination, and high standards of abattoir hygiene.

TUBERCULOSIS OF ANIMAL ORIGIN. While tuberculosis has been recognized as a cause of high mortality in man since the dawn of history, it is only of comparatively recent times that the significance of animal tuberculosis to human health has been fully grasped. Probably the effect of Koch's[59] statement in 1901 that the susceptibility of

man to bovine tuberculosis was uncertain and that if it did occur was extremely rare, was a factor of great importance in minimizing the importance of animal tuberculosis as a source of infection to man.

The causative agents are *Mycobacterium tuberculosis, Mycobacterium bovis* and *Mycobacterium avium,* acid-fast bacilli, which are morphologically identical, but which can be differentiated by cultural and biological tests.

The incidence of human tuberculosis of animal origin is obviously related to the incidence in the animal reservoirs, particularly the bovine. For example, the high incidence of bovine tuberculosis in Great Britain, 17% to 18% in 1945[91], is reflected in the reports of Griffith[37] and Munro[38]. These reports indicated an overall incidence of the bovine type infection in man of approximately 33% in non-pulmonary cases of tuberculosis and 5.8% in pulmonary cases. While the obvious source of infection in these cases is predominantly from infected milk, the extent of the danger to man of acquiring tuberculosis by droplet infection in cattle barns has also been widely recognized[49].

Another factor to be considered, in the possible transmissibility of tuberculosis of animals to human beings is the infectivity of the musculature and other edible tissues of meat-producing animals[27].

The susceptibility of swine to tuberculosis is unique in that this animal is susceptible to all three types. Transmission can occur to man by ingestion of undercooked, infected meat, or by direct contact with infective material, by butchers, meat inspectors or slaughtermen.

While tuberculosis may occur also in the dog, cat and horse, these animals constitute only a minor public health problem.

The symptoms of bovine tuberculosis in man are indistinguishable from those caused by the human type tubercle bacillus and will not be detailed.

Laboratory diagnosis of bovine type tuberculosis in man rests on the isolation, identification and typing of the organism, the details of which are presented by Jensen[47].

The treatment of bovine type tuberculosis in man follows the same general principles as are employed in the treatment of the human type infections. Obviously eradication of the disease in animals is the main control measure to be aimed at and the various methods are summarized by the joint WHO/FAO Expert Group[50]. Most methods of eradication are based on the tuberculin testing of all cattle and the slaughter of reacting animals.

TULAREMIA. Tularemia is primarily a disease of rabbits and secondarily of man and other animals. McCoy[68] in 1911 described a disease among rodents in Tulare County, California, which resembled plague and later isolated the causal organism. Wherry and Lamb[116] were the first to isolate the organism from man and did so from an eye infection.

The causal organism is *Pasteurella tularensis,* a pleomorphic coccobacillus which is non-motile, usually non-capsulated, non-sporulating, Gram-negative and may show bipolar staining. It requires enriched media for growth. It can readily be preserved by storage at low temperatures, and is easily killed by heat, the thermal death point being 56° C. for 10 minutes[10].

Tularemia is widely distributed and has been described in reports from Canada, United States of America, and Mexico on the American continent, from many countries in Europe, and from Japan. Francis[29] has dealt with the epidemiology of the disease in the United States. He indicates that rab-

bits and hares are the main reservoir of infection and quotes an overall infection rate of 1% in those species. From these species man and other animals may be infected by contact, frequently by wound inoculation, and by ticks and other insect bites. Ingestion is also a possible course of infection and primary eye infections due to contamination of the conjunctiva have been described. Tularemia is an occupational hazard and chiefly affects hunters, marketmen, cooks, and housewives who become infected as a result of handling or dressing dead rabbits and other game. Laboratory infections are also common.

The incubation period is about 3 days. The onset is sudden and is characterized by headache, chills, vomiting and fever. The sore at the initial site of inoculation develops and the local lymph nodes become swollen and enlarged. The duration of the disease in uncomplicated cases is 3 to 4 weeks. The dangerous complications include tularemic pneumonia, and meningitis. The mortality rate in the United States of America up to 1946 was 7.4%[30].

Streptomycin, chloramphenicol and the tetracyclines are all effective in the treatment of this disease, streptomycin being the antibiotic of choice.

Immunization of exposed laboratory workers, hunters, and game handlers has been advised[51]. Thorough cooking kills the causal organism but in some areas where the incidence is high in the rabbit population regulations have been introduced prohibiting the sale of rabbits.

LISTERIOSIS. The first record of this organism was made by Murray[75] who isolated it from an outbreak in laboratory rabbits in England. Subsequent reports have indicated a world-wide distribution and a considerable number of hosts including man.

The causal organism[2] is a Gram-positive rod 0.4 to 0.5 to 2.0 microns, with rounded ends, slightly turned in some cases, and occurring singly or in parallel pairs. It is motile and in hanging drop preparations shows a peculiar tumbling motility.

Animals affected by this disease in nature include rabbits, guinea pigs, gerbils, sheep, cattle, goats, horses, pigs, chickens, dogs, lemmings, raccoons, ferrets, chinchillas and voles. The sporadic outbreaks indicate the widespread distribution of the disease but little is known of the method of transmission or reservoir host.

Listeriosis in domesticated farm animals has a higher incidence during the period in which animals are confined indoors and it appears that direct contact plays a considerable part in the spread of the disease in those animals[118]. Experimental studies have shown that animals can be infected through seeding their drinking water with cultures of Listeria[36].

Human infections while usually sporadic can occur as epidemics and *Listeria monocytogenes* can be cultivated in many cases from the throat washings of affected individuals[106]. Isolations have also been effected from the urethra of adult males and from the placenta, cervix and vagina of human and animal females, indicating the possibility of venereal transmission. Seeliger[95] has also suggested the possibility of ingestion infection due to consumption of infected, unpasteurized milk.

In man the cases reported have invariably involved the nervous system, usually associated with encephalitis or meningo-encephalitis and less frequently simulating infectious mononucleosis. Wright and MacGregor[120] have described the pathological picture. The most prominent and constant changes are suppurative meningitis, focal necrosis of the liver, focal pneumonia and splenic engorgement.

The antibiotics of the tetracycline group are the most effective in treatment[28]. Although penicillin and sulphonamides in combination appear to be fairly effective, once severe encephalitic symptoms develop no treatment is of any value. Untreated cases of clinical listeriosis usually terminate fatally.

PASTEURELLA MULTOCIDA INFECTIONS. The significance of *Pasteurella multocida* as a pathogen of animals has been well established. Pasteur[86] isolated the organism in 1880 from chickens suffering from "fowl cholera" and subsequently the organism has been isolated from cases of hemorrhagic septicemia in a variety of hosts including cattle, sheep, swine, rabbits, mice, horses and goats. The occurrence of this organism as a saprophyte of the upper respiratory tract of many of those animals has also been recorded[2].

Pasteurella multocida is a short ellipsoidal rod 0.3 to 1.25 microns in length which may appear singly or in pairs. It is non-motile, Gram-negative and when stained by appropriate methods will show bipolar staining.

Pasteurellosis is a well-established infection of both domesticated and wild animals and as such there is ample opportunity for contact and infection of man. Needham's[77] report of a series of 25 cases in the Mayo Clinic has emphasized the importance of this organism as a human pathogen. Two types of pasteurellosis occur in man, one associated with animal bites or contact and the other without any known obvious cause. Magus[65] has recently indicated that *Pasteurella multocida* has been isolated frequently from human sputum. Meyer[72] feels that *Pasteurella multocida* may remain dormant in the respiratory tract for many months and assume a pathogenic role as a result of some trauma or physiological insult to the host.

The symptoms in cases of animal bite are quite similar[43]. There is a local inflammatory process with an ulcer at the point of the abscess from which *Pasteurella multocida* can be isolated. The pain is severe but there is little or no rise in temperature and no swelling of the lymph nodes. Osteomyelitis can be a complicating factor. The duration of the illness varies from a few weeks to several months.

Cases arising from other than animal contact vary widely and may be severe with sinusitis, pleuritis, and meningitis, the most commonly reported sequelae. In generalized infections the mortality is high.

Diagnosis is based on the isolation of *Pasteurella multocida* from local lesions. Treatment is usually successful with the antibiotics of the tetracycline group.

VIBRIOSIS. *Vibrio fetus*, the etiological agent of vibriosis, was first isolated by McFadyean and Stockman[69] in 1913, who described it as a causal agent of abortion in cattle and sheep. Subsequent reports have indicated the widespread prevalence of the disease in these animals and recently Vinzent[108] has drawn attention to the importance of this organism as a cause of placentitis in the human.

Vibrio fetus is a minute comma-shaped rod on initial isolation, but on subculture long filamentous forms may appear. The organism is difficult to grow on primary isolation, requiring moist enriched media and the presence of nitrogen, carbon dioxide or helium in the atmosphere. Huddleson[42] recommends a special Thiol agar medium. Colonies vary from small 1 mm. convex, translucent forms to light tan colonies, up to 3 mm. in diameter[12].

The disease is world-wide in distribution having been reported in cattle and sheep from many countries in Europe, the American, African and Australasian continents. The overall

incidence is unknown but clinical observation indicates that this disease is a major cause of abortion and sterility in cattle and sheep. The first report of human infection was by Vinzent[109] in 1947 and subsequent reports[110] have appeared by the same author but the significance of the disease in man is difficult to evaluate. Human infections are believed to occur by ingestion of animal products or by direct contact with infected animals. In animals transmission is believed to be venereal in nature.

The clinical disease is confined to pregnant females and in them this infection is characterized by a rapid rise in temperature, rapid pulse with some degree of pulmonary involvement. Uterine contractions develop and the fetus is expelled. Following expulsion of the fetus there is immediate subsidence of symptoms and the patient returns to normal.

Diagnosis is essentially a laboratory procedure; in Vinzent's cases *Vibrio fetus* has been isolated in blood culture from all cases. In animals, isolation has also been effected from the infected fetus and from the vaginal discharges.

The organism is sensitive to most antibiotics *in vitro* but clinical treatment both in animals and man seem to indicate streptomycin as the antibiotic of choice, although treatment is very difficult to evaluate.

As this disease is primarily an infection of animals control rests on the elimination of the disease in animals and the thorough cooking and pasteurization of animal products. Control in animals could probably be based on the same principles as are employed in the control of Brucellosis, testing by means of the agglutination test, and eliminating reactors.

REFERENCES

(1) **Allbutt, T. C.,** and **Rolleston, H. D.:** System of Medicine, 2nd ed. London: Macmillan Co., Vol. II, Part 1, p. 235, 1908. (2) **Alston, J. M.,** and **Broom, J. C.:** Leptospirosis in Man and Animals. Baltimore: The Williams & Wilkins Co., p. 171, 1958. (3) **Baker, J.:** St. Bartholomew's Hospital Report, 1873. (4) **Bang, B.:** Ztschr. Tiermedezin, **1,** 241, 1897. (5) **Barnes, L. A.:** U.S. Naval Med. Bull., **33,** 105, 1944. (6) **Breed, R. S., Murray, E. G. D.,** and **Smith, N. R.:** Bergey's Manual of Determinative Bacteriology, 7th ed. Baltimore: The Williams & Wilkins Co., p. 245, 1957. Iidem: Ibid., p. 405, 1957. (8) Iidem: Ibid., p. 599, 1957. (9) Iidem: Ibid., p. 378, 1957. (10) Iidem: Ibid., p. 400, 1957. (11) Iidem: Ibid., p. 598, 1957. (12) Iidem: Ibid., p. 245, 1957. (13) **Brown, T. McP.,** and **Nunemaker, J. C.:** Bull. Johns Hopkins Hosp., **70,** 201, 1942. (14) **Bruce, D.:** Practitioner, **39,** 161, 1887.

(15) **Carpenter, C. M.:** *In* **Hull, T. G.,** Diseases Transmitted from Animals to Man, 4th ed. Springfield, Ill.: Charles C Thomas, p. 109, 1955.

(16) **Davaine, C. R.:** Acad. Sci., **52,** 220, 351, 386, 1863. (17) Idem: Ibid., **59,** 393, 1864. (18) **Davis, D. H. S.:** Bull. W.H.O., **9,** 625, 1953. (19) **Darlow, H. M., Belton, F. C.,** and **Henderson, D. W.:** Lancet, **2,** 476, 1956. (20) **De Koch, G. W., Sterne, M.,** and **Robertson, E. M.:** J. S. African Vet. Med. Assn., **11,** 4, 1940. (21) **Dolman, C. E., Kerr, D. E., Chang, H.,** and **Shearer, A. R.:** Canad. J. Pub. Health, **42,** 228, 1951. (22) **Doran, J. H.:** Ann. Int. Med., **37,** 714, 1952. (23) **Dumont, J.,** and **Cotoni, L.:** Ann. Inst. Pasteur, **35,** 625, 1921. (24) **Eichorn, A.,** and **Edmonds, A. L.:** J. Am. Vet. Med. Assn., **58,** 278, 1928. (25) **Eisele, C. W.,** and **McCullough, N. B.:** J. Am. Med. Assn., **135,** 1053, 1947. (26) **Evans, A. C.:** U.S. Public Health Service Hygiene Lab. Bulletin No. 143, 1925.

(27) **Fieldman, W. H.:** *In* **Hull, T. G.,** Diseases Transmitted from Animals to Man, 4th ed. Springfield, Ill.: Charles C Thomas, p. 43, 1955. (28) **Finegold, S. M., Bradley, J. G., Campbell, M. K.,** and **Greenbert, A. J.:** A.M.A. Arch. Int. Med.,

93, 515, 1954. (29) **Francis, E.:** Pub. Health Rep., **52,** 103, 1937. (30) Idem: Tr. Assn. Am. Phys., **60,** 181, 1947. (31) **Futaki, K., Takaki, I., Taniguchi, T.,** and **Osumi, S.:** J. Exper. Med., **23,** 249, 1916.

(32) **Gaiger, S. H.,** and **Davies, G. O.:** Veterinary Pathology and Bacteriology, Baltimore: The Williams & Wilkins Co., p. 259, 1955. (33) **Galton, M. M., Menges, R.,** and **Stelle, J. H.:** Ann. New York Acad. Sci., **70,** 427, 1958. (34) **Gartner, A.:** Correspondenzbl. d. aggl. ärztl. Ver u. Thuringen, **17,** 233, 1888. (35) **Graham-Smith, G. S.:** J. Hyg., **41,** 5, 1941. (36) **Gray, M. L., Slafseth, H. J.,** and **Thorp, F.:** J. Am. Vet. Med. Assn., **118,** 242, 1951. (37) **Griffith, A. S.:** Tubercle, **18,** 529, 1937. (38) **Griffith, A. S.,** and **Munro, W. T.:** J. Hyg., **43,** 229, 1944.

(39) **Heeren, R. N.:** New Orleans Med. & Surg. J., **99,** 545, 1947. (40) HOLY BIBLE: Deuteronomy, 14:21. (41) HOLY BIBLE: Exodus, 9:10. (42) **Huddleson, I. F.:** J. Bact., **56,** 508, 1948. (43) **Hull, T. G.:** *In* **Hull, T. J.,** Diseases Transmitted from Animals to Man, 4th ed. Springfield, Ill.: Charles C Thomas, p. 377, 1955.

(44) **Inada, R., Ido, Y., Hoki, R.,** and **Ito, H.:** J. Exper. Med., **23,** 377, 1916.

(45) **Jellison, W. L.:** *In* **Hull, T. J.:** Diseases Transmitted from Animals to Man, 4th ed. Springfield, Ill.: Charles C Thomas, p. 547, 1955. (46) **Jellison, W. L.,** and **Reinhard, K.:** Ibid., p. 522, 1955. (47) **Jensen, K. A.:** WHO Monograph Series: Advances in the Control of the Zoonoses. p. 35, 1953. (48) Joint WHO/FAO Expert Comm. on Zoonoses: WHO Technical Report 169, p. 17, 1959. (49) Iidem: WHO Technical Report 40, p. 5, 1951. (50) Iidem: Ibid., p. 7., 1951.

(51) **Kadull, P. J., Reames, H., Coriell, L. L.,** and **Foshay, L.:** J. Immunol., **65,** 425, 1950. (52) **King, P. F.:** Lancet, **2,** 196, 1946. (53) **Klauder, J. V.:** *In* **Hull, T. G.,** Diseases Transmitted from Animals to Man, 4th ed. Springfield, Ill.: Charles C Thomas, p. 192, 1955. (54) **Klauder, J. V.,** and **Rule, A. M.:** J. Invest. Dermat., **12,** 335, 1949. (55) **Klauder, J. V.:** J. Indust. Hyg., **14,** 222, 1932. (56) Idem: J. Am. Med. Assn., **111,** 1345, 1938. (57) **Koch, R.:** Beit. Morphol. Biol. Pflanzen, **2,** 303, 1876. (58) Idem: Ibid., **2,** 303, 1876. (59) Idem: Tr. Brit. Congr. Tuberc., **1,** 23, 1902.

(60) **Lawson, G. B.,** and **Stinnett, T. S.:** South. Med. J., **26,** 1068, 1933. (61) **Legge, T.:** Industrial Maladies. London: Oxford University Press, 1934. (62) **Levey, J. S.,** and **Levey, S.:** Proc. Soc. Exper. Biol. & Med., **68,** 314, 1948. (63) **Link, V. B.:** Public Health Monograph No. 26: A History of Plague in the United States, 1955. (64) **Loeffler:** Arb. a. d. Kaiserlich Gesundheits, **1,** 46, 1885.

(65) **Magus, M.:** Personal communication, 1959. (66) **McCoy, G. W.:** Public Health Bulletin No. 43, 1911. (67) **McCulloch, E. C.:** Disinfection and Sterilization. Philadelphia: Lea & Febiger, 1936. (68) **McCullough, N. B.:** Ann. New York Acad. Sci., **70,** 541, 1958. (69) **McFadyean, F.,** and **Stockman, S.:** Report of the Departmental Committee of the Board of Agriculture on Epizootic Abortion, 1913. (70) Medical Research Council Special Report Series No. 260, p. 29, 1947. (71) **Meyer, K. F.:** Bull. WHO, **9,** 619, 1953. (72) Idem: Symposium on Unusual Infections of Childhood: Laboratory Tests and Special Procedures, Pediat. Clin. N. America, **2,** 3 to 17, 1955. (73) **Morrill, C. C.:** J. Infect. Dis., **65,** 322, 1939. (74) **Morse, E. U.:** Proc. Am. Vet. Med. Assn., 92nd Ann. Meeting, p. 162, 1955. (75) **Murray, E. G. D., Webb, R. A.,** and **Swann, H. B. R.:** J. Path. & Bact., **29,** 407, 1926. (76) **Murray, T. J.:** J. Infect. Dis., **48,** 457, 1931.

(77) **Needham, G. M.:** Proc. Staff Meet., Mayo Clin., **23,** 361, 1948. (78) **Noguchi, H.:** J. Exper. Med., **27,** 575, 1918.

(79) **Ogata, M.:** Deutsch. med. Wchnschr., **58,** 77, 1908. (80) Osler's Principles and Practice of Medicine, 16th ed. New York: Appleton-Century Co., p. 228, 1944. (81) Idem: Ibid., p. 187, 1944. (82) Idem: Ibid., p. 217, 1944. (83) Idem: Ibid., p. 545, 1944.

(84) **Pollender:** Vertljschr. f. gerichtl. Med., **8,** 1849. (85) **Pasteur, L.:** Compt. rend. Acad. Sci., **91,** 86, 455, 697, 1880. (86) Idem: Ibid., **90,** 239, 1880. (87) **Place, E. H., Sutton, L. E.,** and **Willnes, O.:** Boston Med. & Surg. J., **194,** 285, 1926. (88) **Pollitzer, P.:** Bull. WHO, **9,** 457, 1953. (89) **Pulaski, E. J.,** and **Amspecker, W. H.:** Bull. U.S. Army Med. Dept., **7,** 221, 1947.

(90) **Renoux, G. E.:** WHO Monograph Series No. 19: Advances in the Control of the Zoonoses, p. 61, 1952. (91) **Ritchie, J. N.:** Ibid., p. 25, 1953. (92) **Rosenbach, F. J.:** Ztschr. f. Hyg. u. Infektionskrankli., **63,** 343, 1909.

UNIVERSITY OF MICHIGAN LIBRARIES

(93) **Schottmüller, H.:** Dermat. Wchnschr., **58,** 77, 1914. (94) **Scott, R. B.,** and **Wooding, C. H.:** Paediatrics, **7,** 349, 1951. (95) **Seeliger, H.:** Listeriose. Leipzig: J. A. Barth, 1955. (96) **Simond, P. L.:** Ann. Inst. Pasteur, **12,** 625, 1898. (97) **Sokley, S. S., Wagle, P. M.,** and **Habbu, M. K.:** Bull. WHO, **9,** 637, 1953. (98) **Spink, N. W., McCullough N. B., Hutchings, L. M.,** and **Mugle, C. K.:** J. Am. Med. Assn., **149,** 805, 1952. (99) **Stableforth, A. W.:** WHO Monograph Series No. 19, Advances in the Control of the Zoonoses, 71, 1952. (100) **Stefansky, V. K.,** and **Grünfeld, A. A.:** Zentralbl. f., Bakteriol., **117,** 376, 1930. (101) **Stein, C. D.:** *In* **Hull, T. J.,** Diseases Transmitted from Animals to Man, 4th ed., p. 65, 1955. (102) **Stockard, J. L.,** and **Woodward, T. E.:** Ann. New York Acad. Sci., **70,** 414, 1958. (103) **Strangeways, J. A.:** J. Path. & Bact., **37,** 45, 1933.

(104) **Taylor, R. M., Lisbonne, M., Vidal, L. F.,** and **Hazemann, R. H.:** Bull. Health Org., League of Nations, **7,** 503, 1938. (105) **Torkildsen, A.:** Bull. Hyg., **18,** 1013, 1953.

(106) **Urbach, H.,** and **Schbinski, G.:** Z. Hyg. Infektions Krankh., **141,** 239, 1955.

(107) **Verge, J.:** Rev. gen. Med. Vet., **42,** 65, 1933. (108) **Vinzent, R.:** La presse méd., **81,** 1230, 1949. (109) **Vinzent, R., Dumas, J.,** and **Picard, N.:** Bull. Acad. Nat. Med., **131,** 90, 1947. (110) **Vinzent, R., Delarve, J.,** and **Hebert, H.:** Ann. de Méd., **51,** 23, 1950.

(111) **Walch-Sorgdrager, B.:** Leptospirosis. Bull. Hlth. Org., League of Nations, **8,** 143, 1939. (112) **Weil, H. A.:** Deutsches Arch. f. klin. Med., **39,** 209, 1886. (113) WHO Technical Report Series, 169, 29, 1959. (114) Idem: 34, 1959. (115) WHO Technical Report Series 148, Joint FAO/WHO Expert Comm. on Brucellosis, 3rd Report, 1958. (116) **Wherry, W. B.,** and **Lamb, B. H.:** J. Am. Med. Assn., **63,** 204, 1914. (117) **Wilcox, W.:** Am. J. Med. Sci., **26,** 245, 1839. (118) **Winn. J. F., Cherry, W. B.,** and **King, E. O.:** Ann. New York Acad. Sci., **70,** 624, 1958. (119) **Wolff, J. W.,** and **Broom, J. C.:** Bergey's Manual of Determinative Bacteriology, 7th ed. p. 907, 1957. (120) **Wright, H. A.,** and **MacGregor, A. R.:** J. Path. & Bact., **48,** 470, 1939.

(121) **Zammit, T.:** Mediterranean Fever Commission Report, 1905-1907.

PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

JOHN E. GORDON, M.D.
PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY, EMERITUS
HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH
BOSTON, MASSACHUSETTS

AND

THEODORE H. INGALLS, M.D.
PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY
UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE
PHILADELPHIA, PENNSYLVANIA

RUBELLA: ITS EPIDEMIOLOGY AND TERATOLOGY

BY THEODORE H. INGALLS, M.D.

FRANK L. BABBOTT, JR., M.D.

KENNETH W. HAMPSON, M.D.

AND

JOHN E. GORDON, M.D.

(From the Department of Public Health and Preventive Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania [Ingalls, Babbott]; Directorate General of Medical Services/Air, Royal Canadian Air Force, Ottawa, Ontario, Canada [Hampson]; and Department of Epidemiology, Harvard University School of Public Health, Boston, Massachusetts [Gordon].)

RUBELLA has been recognized as a clinical entity among communicable diseases for at least two centuries[21,85]. However, the efforts of microbiologists to isolate and grow an infectious agent have had limited success. After more than a century of relative obscurity among the common communicable diseases of childhood, the disease achieved a new prominence early in World War II when the far reaching observations of Gregg[32], through a series of 78 infants whose mothers had had rubella in the first trimester of pregnancy, indicated a connection with congenital cataract. The new respect accorded rubella marks a permanent change of attitude on the part of physicians and public alike; and yet actual numbers of cases remain indefinite because the usual mildness of the disease results in reporting being grossly incomplete. Most cases, especially among children, probably never come to medical attention. As a consequence the study of morbidity trends and distributions is hampered. Hope for effective control of the disease rests in development of appropriate laboratory techniques, in the study of experimentally induced infections[9,48] and in improved reporting and further epidemiologic analysis of outbreaks in closed populations, as in schools[13,22,39b], institutions[38] and iso-

UNIVERSITY OF MICHIGAN LIBRARIES

lated communities[36,49b]. The present intent is to assess existing knowledge as a means toward directing future effort in prevention and control.

The Clinical Disease. Rubella is a mild, self-limiting communicable disease of children and young adults induced by a specific virus. Clinically, the infection is manifested by a mild catarrhal injection of the mucous membranes of the upper respiratory tract and a light macular, pin-point eruption of the skin of face, chest, abdomen, thighs and upper extremities. However, the established potential of rubella to cause congenital abnormalities in the offspring of a pregnant woman demonstates that the infection is soundly constitutional and not merely a local disorder of skin and mucous membrane; and yet, often as not, the patient is afebrile[4]. On occasion rubella can give rise to significant signs and symptoms such as fever, malaise, aches and pains of the muscles and headache, particularly in the back of the eyeballs.

A regular manifestation of rubella is enlargement of the posterior cervical, suboccipital or postauricular lymph nodes. The nodes are firm and yield no exudate on needle puncture. An early leukopenia and a subsequent relative lymphocytosis usually accompany infection, but are of little practical help in establishing the diagnosis. The greater gain is through fitting the suspected case into the context of an epidemic, through a history of exposure 2 to 3 weeks previously.

With the exception of fetal damage, the complications and sequelae of rubella are ordinarily insignificant and rare. Neurologic manifestations are the most serious. In 1956, Steen and Torp[76] found in the literature 88 reported cases they were willing to call rubella encephalitis. Subsequent additions bring the total close to 100 as of 1960. Estimating conservatively that approximately half the population gets rubella at one time or another, it is evident that encephalitis is a highly infrequent complication. Until reliable isolation and serologic identification of the virus becomes possible, there is no certainty that the rare case of encephalitis related in time to rubella is anything more than guilt by association.

Except for absence of demyelinization, the pathologic findings are nonspecific and similar to those of encephalitis associated with other acute exanthemata[69]. The appearance of encephalitis seems to be unrelated to the severity of clinical rubella[11], and comes most commonly one to six days following the rash, although neurologic complications have preceded the exanthem. Seventeen of the 88 cases reviewed by Steen and Torp were fatal; however, most authors describe the condition as characteristically of brief duration with a good prognosis for uncomplicated recovery.

Symptoms ranging from transient muscle pains to those indistinguishable from severe rheumatic fever have been observed infrequently after rubella[9], characteristically in adults, with women of childbearing age predominating[43,52, 71]. Small and medium sized joints are most often involved, and duration of symptoms averages about a week[43,51].

Hemorrhagic disturbances occasionally have been associated with rubella. Ackroyd described 3 cases occurring near Bristol, England; one child died[1]. In their review, Steen and Torp found reports of 15 well-authenticated cases of thrombocytopenic purpura following rubella[76]. Prognosis, however, was good, and bleeding usually subsided in a matter of days or weeks. Tadzer from Yugoslavia[83] subsequently reported 6 additional cases. Blood studies of 20 patients with uncomplicated rubella revealed decreased numbers of platelets and increased capillary fragility. The

suggestion is that frank purpura is the severe manifestation of a hemorrhagic tendency present in an undetermined proportion of uncomplicated rubella. On the other hand, as with post-rubella encephalitis, the association may ultimately prove fortuitous.

Except for prenatal mortality, rubella is most infrequent as a cause of death. In Massachusetts[55], 54,387 cases of German measles were recorded in the years 1946 to 1957, but only one death was attributed to this disease. Acknowledging gross underreporting of cases, this gives a fatality rate of 1.8 per 100,000. The United States Army data indicate a death rate of 5.2 per 100,000 for rubella between 1942 and 1945[28]. Thus, while death from rubella does occur, it is an extremely rare event.

Differential Diagnosis. Typical cases developing in the midst of an outbreak offer no diagnostic problem. There is, however, enough variation in symptomatology, signs and the circumstances surrounding the individual patient to raise diagnostic obstacles; more so than in measles, for example. The lack of dramatic pathognomonic features results in a variety of different conditions being mistaken for rubella, especially when cases are scattered and the distribution is endemic[16,19,36,67]. It is equally probable that rubella also is misdiagnosed and sometimes missed altogether, for in mild cases the rash may appear and fade within a matter of hours. Serological advances of the future may be expected to extend the limits of diagnostic accuracy. Until then a goodly number of cases will occur where diagnosis requires a sound clinical and epidemiological experience. Price[68] summarizes the salient features of clinical rubella as follows: ". . . amongst exanthemata . . . (rubella) . . . is distinguished by its long incubation period, short invasive stage, characteristic adenitis, its benign course and time of its seasonal prevalence." Specifically, the following commoner infections may simulate rubella:

Measles is hardly to be confused with rubella because of the shorter incubation period, cough, character of the rash, Koplik spots and greater severity of both signs and symptoms A history of administration of gamma globulin or similar material should differentiate *modified measles* from rubella.

Roseola infantum ordinarily is confined to children under four years of age and commonly those of about one year. Fever of an intermittent type occurs suddenly, sometimes as much as 105° F. or 106° F., and lasts 3 to 5 days. As the temperature drops to normal or thereabouts, a typical maculopapular rash appears on the trunk and later on the rest of the body. It fades rapidly and a characteristic lymphadenopathy is not observed.

Erythema infectiosum is more of a blotchy flush than a fine papular eruptin, and lymphadenopathy is not of the rubella type.

Other blotchy eruptions are sometimes features of infection with Echo and Coxsackie viruses. They have been identified of late years by laboratory tests, but do not mimic the clinical and epidemiological features of rubella that have been observed for two centuries. These newly recognized viral infections and also drug eruptions will confuse the diagnosis occasionally until serological advances make recognition of rubella wholly specific.

Endemicity and Epidemicity. Because of the mild and transient nature of the disease, many patients with rubella are not seen by a physician, especially the second or third case in a family. Even when a physician attends, cases often are not reported, although the precise degree of underreporting has not been established.

UNIVERSITY OF MICHIGAN LIBRARIES

Notification varies with locality, with time and with differing segments of the population. Collins believed reporting to be best when the disease is unusually prevalent.[14].

A study of measles among Denver school children in 1955-56 indicated that 51% of known cases were reported to the health department[18]. Certainly for rubella, a more innocuous disease, an even smaller proportion of cases finds its way into official health statistics. The Division of Communicable Diseases of the Massachusetts Department of Public Health estimates that since 1940 roughly 21% of rubella cases occurring in that state has been reported[66]. This is based on cumulative attack rates described in Collins' earlier survey[14]. However, only long term morbidity studies can give the true incidence of rubella.

Although reporting of rubella is neither complete nor consistent, official statistics do provide useful indications of long-term fluctuations. Figure 1 illustrates incidence of German measles per 100,000 population in Massachusetts by month and year, 1917-1956. As has been pointed out[39c], an interval of about 7 years usually separates epidemic peaks, which are generally preceded by a 3-year build up and followed by a gradual recession in numbers. Three of the 4 largest outbreaks coincided with periods of military mobilization. The effect of social mobility and transportation tempo is evident. Yet the same changes in social mobility, which presumably were largely responsible for reducing the incidence of measles and mumps in the adult population between World War I and World War II, did not have that effect on rubella. The reason appears to be that rubella is much less readily communiable than the other common communicable diseases of childhood. This interpretation is supported by the lower cumulative attack rates and by experience in isolated communities such as Iceland (Table 1) or in boys' schools[13, 22,39b]. In such small or isolated communities outbreaks of rubella follow no recurring pattern. Epidemics are a function of irregular virus introductions and social mobility rather than of a predictable build up of susceptible children which occurs in larger communities where rubella is endemic.

TABLE 1.—REPORTED CASES OF FOUR COMMUNICABLE DISEASES IN ICELAND, 1928–1957

Year	*Rubella*	*Measles*	*Mumps*	*Chickenpox*
1928	18	2,293	0	198
1929	29	3,026	988	157
1930	102	0	1,858	101
1931	368	31	325	184
1932	24	132	4	201
1933	9	0	3	351
1934	3	0	2	315
1935	9	16	0	178
1936	9	8,245	16	256
1937	32	163	1	292
1938	55	1	1	385
1939	8	1	0	292
1940	781	14	1	245
1941	1,566	0	197	133
1942	29	1	5,034	337
1943	94	6,614	601	516
1944	34	540	13	328
1945	12	3	0	299
1946	16	23	4	374
1947	357	4,396	19	351
1948	157	377	397	492
1949	54	2	1,411	435
1950	135	882	925	875
1951	75	5,737	33	1,309
1952	41	1,507	14	750
1953	38	396	12	1,061
1954	2,453	6,573	434	1,201
1955	1,442	1,214	5,977	873
1956	353	7	176	525
1957	73	12	25	1,254

Source: Prof. J. Sigurjonsson, University of Iceland, Reykjavik, Iceland.

Rubella in Military Populations. As a particular problem of military populations, rubella is of no great moment except as it is a potential threat to

wives of service personnel; however, it can be responsible for considerable time lost, especially among recruits. During the first 7 months of 1952 in Fort Dix, New Jersey, 388 hospitalized patients missed 2,400 man days of training because of rubella[74]. German measles ranks well below mumps and measles as a disruptive influence in the military, though in World War II, rubella outstripped these two companion diseases in overall incidence bers of the Royal Canadian Air Force stationed in Canada between 1940 and 1945, measles, mumps, chickenpox, German measles and scarlet fever together comprised 6.4% of all morbidity and 9.8% of all days of hospital care. Rates for mumps and scarlet fever were highest, while chickenpox occurred with the least frequency. Female personnel had an incidence of rubella and measles about 50% higher than their male cohorts[62].

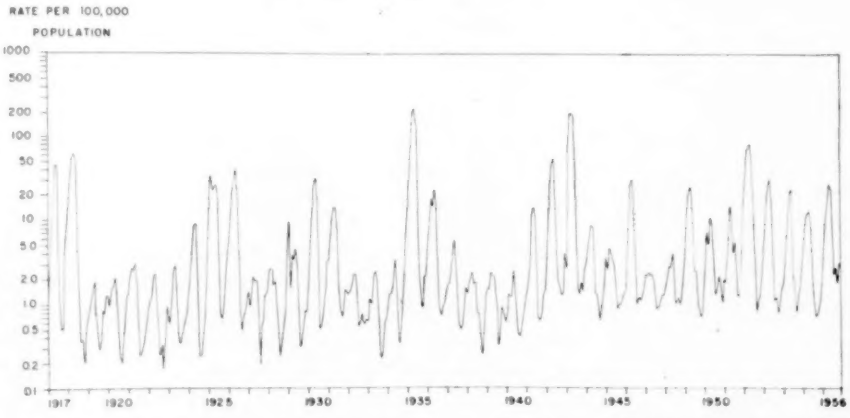

Fig. 1.—German Measles in Massachusetts by Month and Year, 1917-1956 Rates per 100,000 Population. Source: Massachusetts Department of Public Health, Division of Communicable Diseases[55].

which, for the United States Army, was 5.33 per annum per 1,000 average strength[28]. Since rubella occurred most frequently among recruits, high incidence paralleled and followed periods when induction rates were also high. Likewise, the incidence in Continental United States was eight times that for troops stationed overseas. Of all military theaters, Latin America had the highest rate because it included recruits from Puerto Rico[77]. The crowding of troops in staging areas and aboard ship contributed to the comparatively high frequency of outbreaks on transports, a phenomenon also noted in the British Navy[86]. In mem-

Seasonal Distribution. One of the classical features of German measles is the tendency for epidemics to occur in the spring. For example, in New York City, two-thirds of reported cases occurred between April and June for the years 1906 to 1938[15]. Likewise, the half century of data from St. Mark's School shows that only 3 of 30 introductions of rubella occurred in the autumn months[39b]. For the Southern Hemisphere, a mirror image is found when the 1955 data from Australia are compared with those of Massachusetts for the same year. The Massachusetts peak was April and May; the Australian peak came during their

spring in September and October. Lacking adequate vital statistics, it is impossible to determine the monthly behavior of rubella in the tropics. Presumably the year around distribution of cases would be more uniform than at climatic extremes, but the hypothesis is untested.

As expected, the usual seasonal distribution of rubella does not hold under all circumstances. Humphrey and Ekermeyer[38], for example, describe an autumn outbreak in an Ohio orphanage. The virus was introduced to a susceptible population under conditions especially favorable to transmission. About half of 305 exposed children contracted recognized disease and 6% suffered relapse or reinfection.

Host Factors. *Distribution of rubella by age and sex.* Gordon and Hood[29] have pointed out that in most communicable diseases of childhood, attack rates for males exceed those for females, at least until adolescence. Perhaps the more gregarious behavior of boys increases their exposure. Whatever the explanation, this excess of male over female rates in childhood applies in the few instances where rubella epidemics have been studied carefully[36,58].

Official health statistics reveal a less consistent relationship. In Massachusetts between 1920 and 1958, rubella among girls aged 5 to 14 predominated during 24 annual periods, whereas there was a preponderance of reported rubella among boys in 11 years. The sex distribution was about equal in 4 years. Generally, males accounted for a larger share of reported cases in nonepidemic years, and girls during periods of high prevalence.

Children comprise nearly 90% of reported rubella, but clinical concern is almost exclusively with the relatively few cases among females in the childbearing years. The sex distribution of adult patients follows a fairly consistent pattern. Except for 1941, 1942 and 1951, Massachusetts data between 1921 and 1958 reveal an excess of female over male cases among persons aged 20 to 39 years. The 3 years not following this pattern were years when military mobilization brought together large numbers of adult males under circumstances favoring transmission. In more normal times, females are reported to constitute 60 to 70% of adult cases of rubella, perhaps because they are more intimately exposed to the childhood reservoir of infection than the comparable male cohort. One might postulate variations in susceptibility between men and women to account for the difference in attack rates, but in the absence of controlled studies, the simple environmental feature of exposure seemingly suffices.

The excess adult female rates could be interpreted as overreporting in this age group following Gregg's demonstration of the teratogenic properties of rubella. Actually, Massachusetts data suggest that females accounted for approximately the same 60 to 70% of total adult German measles before Gregg's observations as in the years since 1941. The "Gregg effect" on reported adult rubella seems to be more fiction than fact.

The age at which people get communicable diseases was studied by Collins *et al.* in 1935-36. A survey of 200,000 families in 28 large cities revealed that by the age of 15 years, 31% of the surveyed population reported having had rubella. The increase thereafter to the age of 20 was only 1% (Fig. 2). During 1959 data were collected from the parents of 1,390 boys living in greater Philadelphia or Camden County, N.J., and attending two summer camps[6]. In this small sample, 37% reported having had rubella by age 15. The proportion with a history

of rubella in each age group closely approximated that demonstrated by Collins nearly 25 years earlier. The cumulative rates for rubella were much lower than the comparable rates for measles and chickenpox in this same sample of boys, 81% of whom were reported as having had these two diseases by age 15.

Just as there is a difference in the proportion of the population eventually

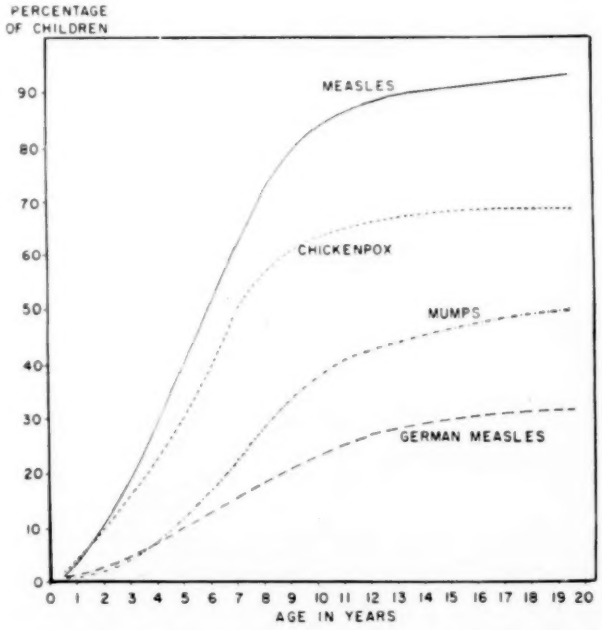

Fig. 2.—Percentages of Young Persons of Specific Ages with History of Prior Attack of Four Common Communicable Diseases. Source: After Collins[14].

getting rubella and measles or chickenpox, so there is a difference in age of attack (Fig. 3). Age specific attack rates for measles and chickenpox show a progressive rise from one year to a peak coinciding with school exposure at five or six. Thereafter, the decline is regular and steep until about age 12, when the curve flattens out and gradually approaches zero by adulthood. The curve for rubella, however, is not characterized by the kindergarten-first grade apex. Rather, there is a mounting attack rate in early childhood, almost a plateau during primary school years, and a gradual decrease thereafter. During and following adolescence, attack rates for rubella exceed those for measles or chickenpox, probably because the population has a greater proportion of susceptibles.

Long-term trends in age distribution. Because of the relationship between rubella and congenital anomalies, it is important to know whether or not adults are accounting for an increasing proportion of cases. The scant evidence fails to give a clear-cut answer, though some data suggest slight changes in recent decades.

As an example, United States Army admission rates for German measles were approximately the same for re-

UNIVERSITY OF MICHIGAN LIBRARIES

cruits in World War II as in the first World War. These figures indicate there was no significant change in the immunity status of young adult males between the two wars. This rubella experience was in sharp contrast to that of mumps and measles, which, during the second World War, fell to one-eighth of World War I levels[29].

The information derived from reported cases of rubella among females in Massachusetts is more equivocal[55]. Women aged 20 to 39 years accounted for a decreasing proportion of female cases in the three 5-year intervals between 1924 and 1938 (Table 2). However, the downward trend was reversed between 1939 and 1943 when 12% of

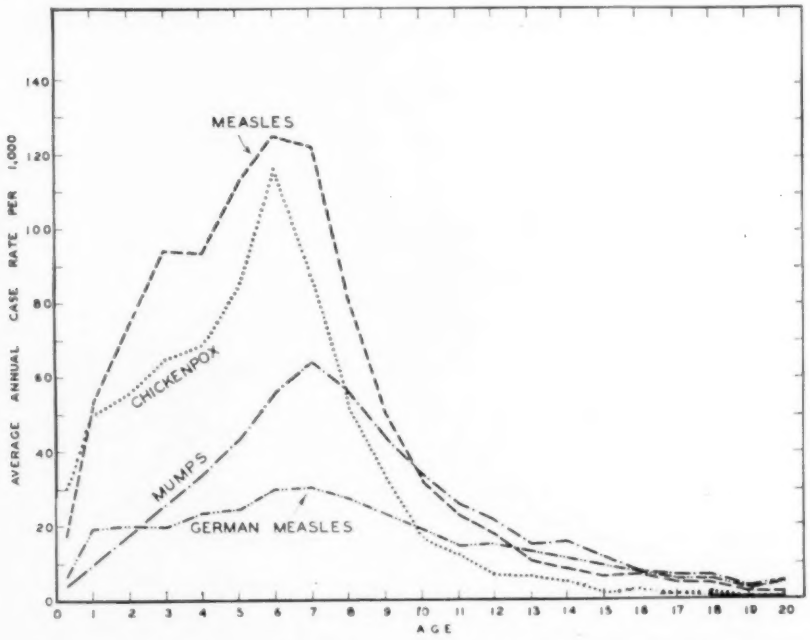

Fig. 3.—Estimated Average Annual Incidence of Four Communicable Diseases among Young Persons of Specific Ages. Source: After Collins[14].

TABLE 2.—RUBELLA IN MASSACHUSETTS, 1924 TO 1958
REPORTED CASES AND PERCENT DISTRIBUTION AMONG FEMALES BY AGE

	Age in Years								
	0–9		*10–19*		*20–39*		*40 & Over*		
Years	*Cases*	*%*	*Cases*	*%*	*Cases*	*%*	*Cases*	*%*	*Total Cases*
1924–1928	4253	54.6	2661	34.1	797	10.2	72	0.9	7783
1929–1933	2920	61.2	1400	29.3	412	8.6	37	0.8	4769
1934–1938	9787	49.4	8274	41.8	1595	8.1	152	0.8	19808
1939–1943	9451	41.4	10492	46.0	2743	12.0	128	0.6	22814
1944–1948	2983	60.3	1454	29.3	462	9.3	47	1.0	4946
1949–1953	8130	54.7	5541	37.3	1023	6.9	173	1.2	14867
1954–1958	9545	52.2	7422	40.6	1113	6.1	205	1.1	18285

Source: Massachusetts Department of Public Health, Division of Communicable Diseases[55].

rubella cases among females occurred in this age group, reflecting the nationwide epidemic of 1943. Following high adult rates during World War II, women in the reproductive age have again accounted for a diminishing share of total rubella through 1958. These data suggest either more immunity or decreasing exposure in the adult population. While the trend may be interpreted cautiously as encouraging, it can not be assumed that the level of adult protection is sufficient to preclude future outbreaks in this important group.

Records since 1900 in a boys' boarding school provide an additional bit of evidence for a changing behavior of rubella. They show that German measles has been introduced more frequently in recent years and, with the exception of the decade 1900 through 1909, the number of cases resulting from each introduction has been decreasing[5] (Table 3). The school health records also indicate that since World War II, an increasing proportion of students contracted rubella before high school age. This history of prior disease and consequent immunity has support in the fact that the average attack rate in six outbreaks between 1900 and 1940 was 19.5%, while the average attack rate for the nine outbreaks between 1940 and 1959 was only 9.3%. Whereas only about half of any graduating class is immune, German measles appears to be reaching this population at an earlier age than in previous decades. The obvious obligation of the medical profession is to encourage this natural trend. There is ample reason to believe that rubella may be reaching younger segments of the population. The process of urbanization and suburbanization is everywhere obvious, as is the effect of aggregation on disease transmission[57]. While the United States population rose by 19.6 million between 1940 and 1950, rural population actually declined by three million[17]. In many sections of the country, the one-room school house has been supplanted by the consolidated school district, to give opportunity for exposure of more children to communicable diseases at an earlier age. With the ever expanding highway system and almost universal use of the automobile for transportation, isolation is no longer a common feature of even small communities. In fact, the country school, theater and shopping center probably bring together as many pathogens and susceptible hosts as do their counterparts in an urban setting. For highly communicable diseases like mumps and measles, these social forces altered age specific rates even three and four decades ago. Their effects on the less communicable disease of rubella may only now be starting to be evident.

TABLE 3.—RUBELLA IN ST. MARK'S SCHOOL, 1900 TO 1960, NUMBER OF TIMES INTRODUCED, NUMBER OF CASES, AND CASES PER INTRODUCTION

Years	*Times Introduced*	*Number of Cases*	*Cases per Introduction*
1900–1909	2	20	10
1910–1919	2	59	29.5
1920–1929	2	41	20.5
1930–1939	4	69	17.3
1940–1949	8	102	12.8
1950–1959	12	65	5.4

Source: Ingalls, T. H.[39b].

Race. No particular ethnic group is known to be immune to German measles. Recent world-wide reports confirming the association between rubella and congenital anomalies attest to the universal susceptibility of people wherever the disease is introduced[8,41,44,50,82]. Nevertheless, the incidence of reported German measles is not neces-

UNIVERSITY OF MICHIGAN LIBRARIES

sarily the same for all ethnic groups even in the United States. By way of illustration, rubella attack rates for the first six months of 1952 in Fort Dix, New Jersey, were more than twice as high among white recruits as for their Negro cohorts, 45.6 per 1,000 per year against 17.2 per 1,000 per year[74]. However, the authors point out that most soldiers reported on sick call only when they noticed the rash, and the transient rash was much less obvious on the pigmented skin. Thus, a paucity of diagnostic signs rather than the absence of disease may have influenced the differing reported attack rates. Apparently, however, there is less disparity between urban white and Negro children than in the adult military population just mentioned. Recent experience for rubella in the city of Philadelphia suggests that the disease is occurring at comparable rates in both major racial segments of the childhood population[23].

Immunity to Rubella. Whereas both rubella and measles generally produce durable immunity[2a,69], second attacks appear more frequent with rubella. In the Falkland Islands outbreak studied by Hillenbrand[36], 15 of the 33 pregnant women who became ill claimed to have had rubella prior to this epidemic, as did 15 of 107 school children. The same author, reviewing 88 cases of rubella in a London hospital, found that three had been admitted to the same institution with the same diagnosis at an earlier date. A review of school health records[39b] and the experience of practicing physicians, likewise confirm the lay impression that an attack of rubella does not necessarily preclude subsequent experience with the same illness. However, there are no reliable statistics from which rates of second attack can be derived and one attack generally produces immunity. As in measles, and unlike the situation in pertussis[29], maternal antibodies against rubella provide the newborn infant with protection for the first few months of life[56].

Relapse, defined as a return of symptoms during convalescence, is a phenomenon of some frequency in rubella. Humphrey and Ekermeyer[38] reported 18 relapses in 306 cases occurring from 12 to 43 days after onset of first attack. Two relapses 15 days following disappearance of the rash were observed by Michael in another institutional outbreak[58], and Geiger reported 15 relapses among 173 cases 3 to 5 weeks after first attack[26].

Rubella Without Rash. An equally interesting host reaction is the absence of rash in an otherwise characteristic case of German measles. Hiro and Tasaka[37] noticed fever and lymphadenopathy but no rash after the appropriate incubation period in 2 of 16 children receiving nasal washings from an active case. Similar observations on monkeys were made by Habel[33]. Anderson[2a] felt there was good evidence for atypical cases of experimental rubella, as did Krugman *et al.*[48] using human volunteers.

However, atypical disease also has been reported for rubella transmitted under natural conditions. Habel[33] describes two physicians' sons who were definitely exposed to German measles and who came down with fever, malaise and posterior cervical adenopathy, but no rash, 17 and 18 days later. Flöystrup[24] relates a similar story for his boy, the only difference being that a second child in the family contracted typical rubella following exposure to the rash-free brother. On the basis of persistent lymphadenopathy, low or absent fever, but no rash, Hillenbrand estimates that approximately one-third of the Falkland Islands cases were of the atypical variety[36]. Whatever the explanation for this observation, it is unlikely that it resulted from a less pathogenic agent. On the other hand,

it is probable that a careful study of most epidemics would reveal a clinical gradient of disease. Morbidity data from Massachusetts indicate that only about 10% of rubella cases occur in adults, and yet some 60% of adults deny ever having had the disease. Subclinical infection may play a greater part in population immunity than the small number of recognized atypical cases would suggest. The whole subject of immunity warrants further attention in order to understand why the babies of more than half the women who contract rubella in early pregnancy escape without congenital stigmas.

In this regard, an important biological problem may be to determine the immunologic status of the fetus whose mother has contracted the infection in pregnancy. An approximation of this kind of information is provided by a group of "rubella children" in England, whose postnatal histories were made available to us[25]. Of 19 "rubella children" born during or after 1950 (15 were born from 1950 to 1954 inclusive) 3 had had rubella as of the end of 1958, whereas 4 of their next older siblings and 2 of their next younger siblings had had rubella by this time. These findings do not suggest that maternal rubella in the first trimester of pregnancy results in postnatal immunity of the conceptus. These children are still under observation.

The Infectious Agent. The viral etiology of rubella was first demonstrated conclusively by Hiro and Tasaka in 1938[37]. They produced clinical German measles in 6 out of 16 children inoculated with infective nasopharyngeal secretions passed through Berkefeld W and Seitz E-K filters. After appropriate incubation periods, 2 additional children developed mild illness although rash was absent.

The susceptibility of primates other than man was first suggested in 1914 by Hess[34] who produced a febrile response in a small series of *Macaca mulatta* monkeys injected intraperitoneally with blood from human cases of rubella. Habel in 1942[33] confirmed and extended these earlier observations using infective nasal washings and defibrinated blood as source material. Successful transmission occurred in 12 of 15 rhesus monkeys, 9 having a transient rash accompanied by pyrexia.

Since 1940, several investigators have used either nasopharyngeal secretions or serum from patients with active rubella to induce infection in susceptible human volunteers. Anderson in Australia[2a] accomplished this by spraying filtered throat washings on the pharyngeal mucosa. The incubation period was 13 to 19 days. Other susceptible individuals became infected by contact with those experimentally infected. Krugman and his colleagues[48] obtained similar results using both blood and nasopharyngeal washings from a patient with rubella, but incubation periods were slightly shorter, between 12 and 16 days, regardless of route of transmission. Recent unpublished data from Tulane University School of Medicine[75] provide further evidence that rubella can be transmitted almost at will by intramuscular inoculation with serum of rubella patients taken shortly after appearance of the rash. The pharyngeal sprayings of infective throat washings likewise produced clinical disease, although with less consistency.

The virus of rubella has generally been considered to enter the body through the upper respiratory tract; indeed, several studies using human volunteers confirm this hypothesis. However, in 1954, Papp reported a unique series of experiments involving transmission of communicable diseases to susceptible children by conjunctival instillation of infective material[64a]. The

UNIVERSITY OF MICHIGAN LIBRARIES

transfer was most easily accomplished with measles, but Papp also induced rubella in 2 of 10 susceptibles by this method. Subsequently, protection of exposed children using convalescent serum dropped in the eye provided further evidence that rubella, as well as other infectious diseases, may be transmitted through the intact conjunctiva[7,64b,72].

The sequence of events following virus entry is not clear. Early in the incubation period, virus particles probably multiply in some unidentified site prior to release in the general circulation. At least in measles, injection of virus directly into the blood stream shortens the incubation period by about 4 days, suggesting that the virus spends the first few days elsewhere than in the general circulation[64b]. Hess has noted that the blood of children exposed to rubella shows a relative reduction in the polymorphonuclear series during the first week of incubation[34]. Other investigators describe an increase in monocytes and plasma cells[12,20,36]. At this stage, Papp postulates for measles that the virus is multiplying in the leukocytes. Finally, towards the end of the incubation period, there is a demonstrable viremia and, more important from the standpoint of disease propagation, virus appears in the nasopharyngeal secretions, thus permitting the infectious agent to escape to a new host.

Reagan *et al.*, examining specially prepared serums of rhesus monkeys infected with rubella, described round virus particles having a diameter of 150 to 160 μ. Occasionally, these particles had an irregular contour. Studies of concentrated serums from control monkeys by electron microscopy, failed to demonstrate similar bodies[70]. These observations have thus far not been confirmed.

The demand for an immunizing agent capable of inducing active immunity in young women has not been met because of inability to maintain rubella virus in serial cultures. Habel[33] carried four strains of virus through five passages on the chorio-allantoic membrane of chick embryos. This material produced in one monkey leukopenia and rash after 14 days and, in a second monkey, fever and leukocytosis without rash and no demonstrable illness in 2 other animals. More recently, Anderson[2b] undertook to isolate the virus in monkey kidney tissue. Between the fifth and ninth passage, large numbers of multinucleate areas were noted in the kidney cells. He also demonstrated the presence of a transmissible agent inactivated by rubella convalescent serum.

Subsequently, Anderson[2c] has grown rubella virus producing cytopathogenic changes after five passages on monkey kidney tissue and inducing mild, transient exanthema and lymphadenopathy when sprayed into the throats of 3 out of 8 presumably susceptible human volunteers. However, the irregularity with which the agent was maintained in tissue culture prompted him to discontinue the experiment. Other workers have had similar difficulties.

Until the virus can be studied carefully *in vitro*, little certainty is possible about its properties. There is general agreement, however, that it survives prolonged exposure to cold[2a,b,48,70]. Infective throat washings used by Anderson, for example, had been stored 2 years at $-70°$ C.

When Gregg and other Australian investigators related congenital anomalies to rubella, there was speculation as to this being due to an increased virulence of the virus concerned. The same question has arisen following epidemics where complications appeared unusually prominent. To date no one has demonstrated fluctuations in the

virulence of the infectious agent. The signal contribution of many observers, however, has been to confirm teratogenicity of "street virus," so to speak, for the susceptible host, women who have no immunity and their babies.

Environment and Rubella. Data from Massachusetts, Australia, New York City and St. Mark's School have already been used to demonstrate the high springtime prevalence of rubella. It is still speculative whether this phenomenon relates to seasonal changes in host physiology[3,59], to social factors such as crowding, or to climatic conditions favoring preservation and spread of the virus.

Geography influences the epidemiology of rubella, at least insofar as it determines opportunities for exposure. For example, nation-wide outbreaks of rubella in Iceland during the last 30 years have been limited to the periods 1940-1941 and 1954-1955 (Table 1). Unquestionably geographical isolation contributed to the low prevalence of German measles prior to World War II as it did in Australia. Unquestionably also, the more rapid contact by airplane and ship with areas where rubella is endemic helped kindle the 1940-1941 epidemic, whereas the social and geographic factors which played a determining role in the 1954-1955 outbreak can not be discerned. Collins[14] found considerable variability in the percentage of people between age 15 and 20 years giving a history of having had rubella. In general, rates were lowest in the south (14%) and highest in the western and north central states (30%). Among college students, there was a similar geographic difference, 34% from the south and 48% in the west recalling an attack of German measles. Women consistently reported more rubella than did their male cohorts. Collins was not prepared to say whether these differences were due to chance, survey technique, or geographic variation. He noted, however, in his study of the five infectious diseases of childhood, that the more communicable the disease, chickenpox for example, the less the geographic variability in history of prior illness.

Rubella in Pregnancy. Due to the retrospective nature of the observations that first brought the teratogenic effects of maternal rubella to medical attention, it was impossible to assess the capacity of the virus to interrupt pregnancy. Even during subsequent years, not a great deal has been learned of such risks because of the small numbers of cases that come to the attention of any single observer. However, in 1946 Aycock and Ingalls[4] expressed the opinion that death of the conceptus may represent the extreme effect of maternal infection in early pregnancy. They presented the case histories of 4 women whose babies had died before term and after the mother's rubella. By 1948 Swan[79b] had reviewed 760 stillbirths in South Australia occurring between 1943 and 1945, and found 16 instances of maternal rubella, 13 during the first trimester of pregnancy. These findings indicated clearly that the extreme effects of maternal infection during early pregnancy are manifested in death of the conceptus, a risk that can be computed to be of the order of 10%[10,31,35,40,63].

Prematurity. Clinical and embryological evidence shows a continuum between abortion, miscarriage, stillbirth and prematurity but it is difficult to disentangle the multiple factors responsible for these four phases of disordered development. An unusual opportunity to appraise the relation of rubella to prematurity has been made available to us through observations of a group of handicapped children whose mothers had had rubella in early pregnancy. Birth weights recorded for the

UNIVERSITY OF MICHIGAN LIBRARIES

9 "rubella babies" averaged 5 pounds 15 ounces. This figure compares with 7 pound 15 ounces for 10 of their next older or next younger siblings, the rubella babies averaging 2 pounds lighter. This finding is consistent with the clinical observations of Gregg, Swan and their colleagues that as a group, post-rubella babies were of small size and difficult to feed. The original Australian data do not allow for sibling comparisons but they furnish measurements indicating that the "rubella babies" are significantly lighter than would be expected and they also permit an appraisal to be made of prematurity by length of gestation as well as by birth weight. When both variables are considered together, rubella in the first trimester of pregnancy emerges as a cause of prematurity, whether judged by length of gestation or birth weight.

Congenital Anomalies. The importance of an improved understanding of the epidemiology of rubella comes from the proven capacity of the infection, when it is acquired by a woman during early pregnancy, frequently to deform the unborn child. However, despite careful study of the pathogenesis of these effects for nearly two decades, the way that fetal defects are brought about remains a matter of speculation. Whether disordered growth of the embryo results from direct infection of differentiating cells or from disease of the terminal branchings of a growing capillary tree, or from competition between cells and virus for oxygen or metabolites, is not known. Even the task of quantitating specific risks for the fetus has taken years to accomplish, and is only partially completed for such defects as cataract, deafness and congenital heart disease.

The first observations indicating that maternal rubella in the first trimester of pregnancy may produce congenital deformity in the fetus were reported by Gregg and his colleagues in Australia during the first two years of World War II[32,82]. It is difficult to exaggerate the importance of this discovery for those interested in the pathogenesis of "monstrosities," congenital malformations and of anomalous growth in general. Before 1940, major anomalies and syndromes of a kind that comprise a readily recognizable deformity such as mongolism, tracheoesophageal fistula or congenital heart disease were usually interpreted as expressions of faulty germ plasm. "Faulty germ plasm" is an impressive phrase, but does not commit the user to any stand on whether he thinks the fault is transmitted to the embryo through its quota of genes and chromosomes, or whether it is acquired after fertilization of the zygote; and if so, how. After the Australian epidemics of rubella in 1939 and 1940, it became clear that maternal German measles during the second month of pregnancy could induce congenital cataract, heart disease or deafness in fetuses, most of whom started life in all probability with a normal complement of genes and chromosomes and perfectly good "germ plasm."

Since German measles was accurately described in English in the Edinburgh Medical and Surgical Journal as long ago as 1840[65], it is pertinent to speculate why it was that the simple cause and effect relation between this maternal infection and congenital defects had not been recognized earlier. The answer probably lies in the fact that rubella is commonly a childhood disease with epidemic cycles of the order of 6 or 7 years (Fig. 1). Under average conditions, relatively few adults are susceptible, only half of them are women, and perhaps half of these are married. Not more than a quarter of the married women would be pregnant at any one time and of these only a

third would be in the first trimester of pregnancy. Moreover, only 25 or 30% of women with first trimester rubella would experience the delayed impact of the infection; the risks that their babies ran would be variable and recognition of the rubella stigmas would ordinarily be delayed many months or even years.

However, in Australia in 1939, the stage was set for rubella to make the rounds of the young married set in a way that seldom occurs. Most importantly, there had been no major outbreak of rubella in Australia for 17 years before 1939 when the British Commonwealth went to war. The combination of mass movements of population groups against a background of three missed cycles of the disease assured a countrywide and epidemic spread of rubella when it broke out in 1939 and 1940. An unusually large number of pregnant susceptibles were ready to contact the disease, and in fact did just that during the wartime epidemic. The result was the famous crop of babies born with defects in 1940 and 1941.

Rubella and Congenital Ocular Defects. Gregg's now classic report was of a series of 78 infants with congenital cataract, whose mothers, with few exceptions, had rubella early in the second month of pregnancy. In a later study, Swan and Tostevin[80] confirmed the association and drew attention to the relation of maternal rubella to congenital heart disease and to congenital deafness. Subsequently, Swan, Tostevin and Black[81] made a final assessment of the stage at which the mother had had the infection and again emphasized the relation between the timing of maternal rubella and the kinds of anomaly subsequently observed in the newborn infant. Cumulatively, these observations served to set the stage-specific period for congenital cataract at about the fifth week of pregnancy, a finding never since challenged. This defect was determined pathologically[79a,84] to result from defective development of the fetal nucleus of the eye. The significance of fifth-week timing of the antecedent maternal infection is assuredly related to the state of lenticular differentiation at that time[39a]. Mann[54] has pointed out that the period of active differentiation of the primary fibers that fill the optic lens commences around the fifth to eighth week of gestation. When 29 children whose mothers had had rubella in the first trimester of pregnancy in 1951 and 1952 were followed by Lundström and Boström, and examined ophthalmologically during childhood[53], 2 were found to have congenital cataract and 6 had evidence of an old chorioretinitis. On the basis of this small series, these investigators estimate that the specific risk of developmental ocular defects following first trimester rubella is of the order of 25% in surviving children. Further, they observed that, whereas cataract was a specific risk of maternal infection during the first month of pregnancy, chorioretinitis was more often due to rubella in the second month. Three of the children studied were unable to stand alone in the second year of life, and at least 2 also had impaired hearing.

Rubella and Congenital Heart Disease. One of the more serious groups of anomalies following maternal rubella is congenital heart disease. Such defects were recognized in 3 of Gregg's series[32] of 78 infants with congenital cataract. Similarly in the confirmatory studies of Swan, Tostevin and Black[81], the finding of congenital heart disease was observed again and again and in association with both cataract and deafness. Although the implications of these associations and of the timing of materal infection in pregnancy was that

UNIVERSITY OF MICHIGAN LIBRARIES

congenital heart disease originated during the sixth to ninth week of embryonic development, the data threw little light on the time of origin of particular types of congenital heart disease. It is wholly understandable that until techniques of intracardiac catheterization were introduced as an aid to medical diagnosis, few observations could be made about the morphologic nature of post-rubella cardiac malformations. Provocative has been the frequency with which the infection preceded recognized patent ductus arteriosus; in 14 of the 17 patients with congenital heart disease described by Gibson and Lewis[27], in 20 of 25 patients reported by Rutstein *et al*,[73]. and in 13 of 27 patients studied by Stuckey[78]. It must be borne in mind that these cases are highly selected, for the patients were referred to hospitals for diagnostic study and to surgical clinics for operative therapy. The observations have seemed to be paradoxical because they relate rubella early in pregnancy to arrested closure of a structure normally due to involute after birth. However, as the matter is studied more intensively, more reasons emerge for believing that patent ductus arteriosus may be secondary to increased pressure in the pulmonary bed and to other anomalies caused by maternal rubella[39d].

Rubella and Deafness. The capacity of maternal rubella to cause congenital deafness was recognized after the Australian outbreak of 1940 and Murray[61], in 1949, described audiometric tests which revealed low tone deafness in 105 children whose mothers had the infection in the first half of pregnancy. Lancaster[49a] was able to show that in addition to 1940 and 1941, the years 1924 and 1925, and 1898 and 1899, were times of birth of unusually high numbers of children later to be admitted to institutions for the deaf and dumb in New South Wales. There is little reason to doubt that these crops of deaf children appearing over two successive years represented the toll of maternal rubella.

Further study by Lancaster[49b] of census and institutional data in other countries throws light on the relation of rubella to congenital deafness. He examined census figures in New Zealand, England, Canada, the United States, Sweden and Iceland for evidence of deafness experienced on an epidemic scale. No dramatic findings in any of these countries could compare with the wartime epidemics of rubella-caused deafness in Australia. However, small "outbreaks" were apparent in the vital statistics of the United States, England, Sweden and Iceland. These Icelandic data have been brought up-to-date here through information kindly furnished by Dr. Vilm Jonsson. In addition to the 10 cases of deaf mutism previously noted in the wake of epidemic rubella in 1941, a cluster of 7 cases has thus far been identified following the 1954 epidemic (Fig. 4). The findings in Iceland coupled with those in Australia, establish the association between rubella and congenital deafness so firmly that their linkages in time and place become expected functions of case finding and reporting. This is also the implication of Ivstam's[41] finding in Sweden that a correlation could be demonstrated between the annual incidence of rubella in Swedish armed forces and the frequency with which children were born who were later identified as deaf mutes.

Despite abundant proof that maternal rubella causes congenital deafness, the pathogenesis of the disturbance remains obscure. Kelemen and Gotlib[45] could find no characteristic lesion in the hearing organs of 4 fetuses coming to necropsy shortly after their

mothers had had rubella in early pregnancy. However, one patient had massive hemorrhage in one vestibular scala and another had blood mixed in the mesenchyma of the perilymph; and Gray[30] found lysis of the epithelium of the organ of Corti after infection during the eighth week of pregnancy. Presumably, the lesion is due to partial destruction of the organ of Corti accompanied by hemorrhage and focal necrosis which occurs unperceived in the conceptus at the height of the maternal disturbance. The more time that elapses between this infection and histologic examination of the fetal tissue, the less likely the expectation of finding pathological manifestations of the acute stage of maternal-fetal infection.

Recently, a nation-wide prospective inquiry by Jackson and Fisch in England[42] produced unexpected results. No less than 30.4% of the 57 children whose mothers had rubella during the first 16 weeks of pregnancy were found to have some degree of deafness when hearing was tested at about 4 years of age.

Summary of Risks. The results of all prospective "follow-up" studies undertaken since the rubella hazard was first identified have been to soften the harshness of first judgments. The great advance in 1941, and its significance can hardly be overestimated, was of a qualitative kind: the "trivial" little childhood disease of German measles, when contracted by a mother in early pregnancy, frequently blights the tiny conceptus for life. It is hardly surprising that miscalculations were made in a first attempt to assess risks since the only possible data were of a retrospective nature. Because all post-rubella congenital defects are associated with maternal infection, the "risk" approaches 100% if an attempt is made to calculate it in retrospect. An analogy might be drawn with streptococcal disease and scarlet fever. Patients with

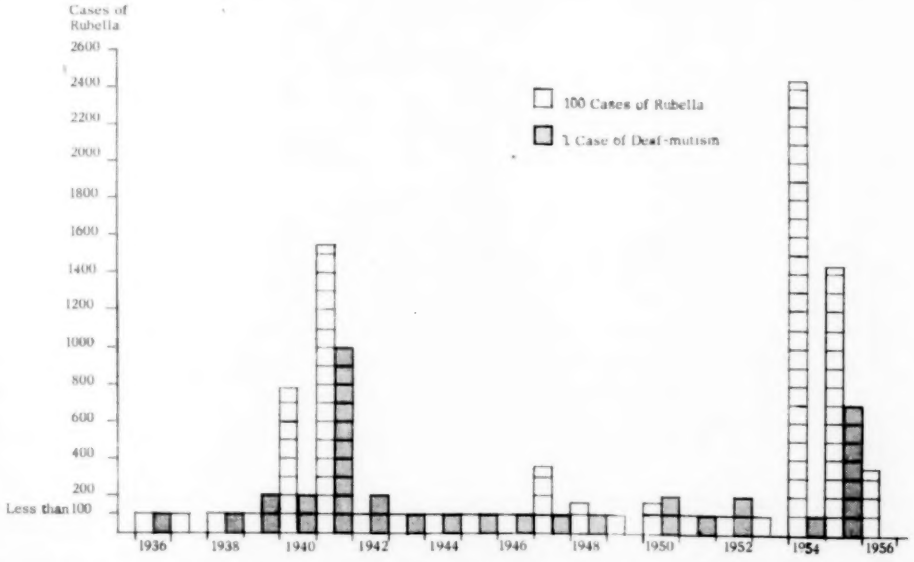

Fig. 4.—Cases of Rubella, Iceland, 1936-1956, and Admissions to the State School for the Deaf and Dumb by Year of Birth. Source: Jonsson, V.[44].

UNIVERSITY OF MICHIGAN LIBRARIES

scarlet fever have generally had streptococcal infection, but the risk of getting scarlet fever can only be determined by a prospective follow-up of patients with streptococcal disease.

Prospective investigations of the past decade set the risk for congenital anomalies of all kinds at about half the 30% figure given by Jackson and Fisch[42] for deafness alone. However, these conservative estimates ordinarily applied only to gross structural malformations, those readily detected by simple physical examination. The increased prevalence of defects evident in the British figures undoubtedly reflects a more thorough screening, and deferral of hearing tests until the children were old enough to cooperate. Probably in the long run this more gloomy prognosis will be reinforced further by deferred examinations of other organs which are not subject to direct inspection at birth. Such congenital lesions as horseshoe kidney or aneurysms of the circle of Willis would hardly be picked up in the neonatal period, in infancy or in childhood. Moreover, mental retardation is known to be a significant risk of maternal infection during early pregnancy, although quantitation of that risk is rendered extremely difficult since milder forms of the defect defy objective measurement. Nor would many forms of congenital heart disease be diagnosed accurately until much time had elapsed, or perhaps not until an operation or necropsy were performed.

Prevention and Control of Rubella. The practical challenge that lies ahead is not repeated confirmation of the harmful effects of maternal rubella; rather it is to provide methods of protecting girls and young women against the disease before they reach childbearing age. In all probability this will take the form for the most part of accepting the offer of natural immunity when the disease is epidemic. For the time being, "rubella parties" would seem a reasonable recommendation to parents of young girls who have not contracted the disease in the natural course of events in their early years. Such parties have been staged with success in parts of England and the United States. Once the family physician has made the diagnosis of rubella in a young girl, the event is used to signal a social occasion for some of her friends, the same day, in order to take advantage of her period of infectiousness. To be sure, precautions are to be taken that unwanted cases are not propagated along the way. On the other hand, the decision at present usually is allowed to go to nature by default. Even today the average age of infection with rubella is uncomfortably high, unlike that for measles, mumps and chickenpox. Despite the fact that the risk of German measles was identified almost 20 years ago, little progress has been made toward purposeful control.

One practical aspect of control has to do with the pros and cons of passive immunization. Krugman and Ward[47], after exploring this matter at length, have advanced strong evidence that gamma globulin, prepared from the plasma of persons convalescent from German measles, contains antibody effective in neutralizing the virus. The finding lends validity to the work and interpretations of Korns[46] who found that one lot of immune serum globulin was highly effective in reducing the risk of infection after exposure when given intramuscularly to exposed persons; another lot had little effect. Korns interpreted his findings to reflect a varying antibody content in different batches of serum globulin. More recently gamma globulin was shown to reduce the incidence of rubella by 70% in controlled studies

among school children of Taiwan[30a]. The duration of protection was estimated at approximately 12 weeks.

Krugman and Ward[47] advise that all pregnant women in the first trimester of pregnancy, and having no known history of previous infection, be given at least 20 ml. of gamma globulin as soon after present exposure as possible. The indications seem particularly clear for the expectant mother whose own child provides the exposure to rubella. The date and time of exposure are known, and the course of action is both evident and rational. Difficulties arise, however, when the history is of casual exposure or the diagnosis itself is in question or of such dubiousness as to make the probability of spread altogether unlikely. An additional obstacle is that rubella is relatively "capricious" in its capacity to spread as compared with measles. A child coming down with measles, for example, will usually transmit the infection to a susceptible sibling sleeping in the same room. The risk of transfer, although significant, would be nowhere as great with rubella. The difference is reflected in age specific and cumulative attack rates of the two infections (Figs. 2 and 3). The principle is also dramatically illustrated in the Iceland data (Table 1).

Over the years, with increased population mobility and hence increased opportunity for human contact, measles has "gone down" into the grade and nursery schools, whereas rubella continues to plague the high schools, colleges and young adults, including young married women. Passive immunization may be a useful aid for a threatened mother. However, such procedure is neither a desirable nor practical solution to the problem of rubella. Rather, infection followed by natural immunity, in persons under the age of 20 will remain the preferred public health objective of the future. Evidence has been presented that this is occurring spontaneously but that nature's trend needs a helping hand from virologists, clinicians and epidemiologists.

REFERENCES

(1) **Ackroyd, J. F.:** Quart. J. Med., **18,** 299, 1949. (2) **Anderson, S. G.:** (a) J. Immunol., **62,** 29, 1949; (b) Lancet, **2,** 1107, 1954; (c) Ibid., **1,** 1043, 1957. (3) **Aycock, W. L.:** Am. J. Med. Sci., **209,** 395, 1945. (4) **Aycock, W. L.,** and **Ingalls, T. H.:** Ibid., **212,** 366, 1946.

(5) **Babbott, F. L., Jr.,** and **Rodenberger, B. M.:** Unpublished data. (6) **Babbott, F. L., Jr., Green, G. R.,** and **McGarvey, J. F.:** Unpublished data. (7) **Banks, H. S.:** Lancet, **2,** 518, 1958. (8) **Bell, J.:** Brit. Med. J., **1,** 686, 1959. (9) **Bennett, R. A.,** and **Copeman, W. S. C.:** Ibid., **1,** 924, 1940. (10) **Brawner, D, L.:** J. Med. Assn. Georgia, **44,** 451, 1955.

(11) **Cantwell, R. J.:** Brit. Med. J., **2,** 1471, 1957. (12) **Carroll, J. V.:** Lancet, **1,** 182, 1934. (13) **Cheeseman, R. A.:** Epidemics in Schools. Med. Res. Council Sp. Rep. Series No. 271. London: H,M. Stationery Office, 1950. (14) **Collins, S. D., Wheeler, R. E.,** and **Shannon, R. D.:** The occurrence of whooping cough, chickenpox, mumps, measles and German measles in 200,000 surveyed families in 28 large cities. Washington, D.C.: Public Health Service Division of Public Health Methods, Special Study Series No. 1, 1942. (15) Columbia University, Delamar Institute of Public Health: Population, births, notifiable diseases and deaths, assembled for New York City, 1866-1938. (16) Control of Communicable Diseases in Man: 9th ed. New York: American Public Health Association, 1960. (17) **Cook, R. C.:** Where Population Growth Hits You. Nation's Business, March, 1957. (18) **Corliss, B. M.:** Thirty-first Annual Report of the Health Service Department, Denver Public Schools, 1955-56. (19) **Cushing, H. B.:** Canad. Med. Assn. J., **17,** 905, 1927.

UNIVERSITY OF MICHIGAN LIBRARIES

(20) **Downey, H.**: Ed. Handbook of Hematology. New York: Harper and Bros., p. 2667, 1938. (21) **Emminghaus, H.**: Jahrb. f. Kinderh., **4**, 47, 1871. (22) Epidemics in Schools: Med. Res. Council Sp. Rep. Series No. 227, London: H.M. Stationery Office, 1938. (23) **Fish, S.**: Personal communication, 1959. (24) **Flöystrup, G.**: Brit. J. Child. Dis., **20**, 20, 1923. (25) **Freeman, P.**: Personal communication, 1959. (26) **Geiger, J. C.**: J. Am. Med. Assn., **70**, 1818, 1918. (27) **Gibson, S.**, and **Lewis, K. C.**: A.M.A. Am. J. Dis. Child., **83**, 317, 1952. (28) **Gordon, J. E.**: General Considerations of Modes of Transmission. Chapter 1 in Preventive Medicine in World War II. Washington: Government Printing Office, vol. 4, 1958. (29) **Gordon, J. E.**, and **Hood, R. I.**: Am. J. Med. Sci., **222**, 333, 1951. (30) **Gray, J. L.**: Ann. Otol. Rhin. & Laryng., **68**, 170, 1959. (30A) **Grayston, J. T.**, and **Watten, R. H.**: New England J. Med., **261**, 1145, 1959. (31) **Greenberg, M., Pellitteri, O.**, and **Barton, J.**: J. Am. Med. Assn., **165**, 675, 1957. (32) **Gregg, N. M.**: Tr. Ophth. Soc. Australia, **3**, 35, 1941. (33) **Habel, K.**: Pub. Health Rep., **57**, 1126, 1942. (34) **Hess, A. F.**: Arch. Int. Med., **13**, 913, 1914. (35) **Hill, A. B., Doll, R., Galloway, T. McL.**, and **Hughes, J. P. W.**: Brit. J. Prev. & Soc. Med., **12**, 1, 1958. (36) **Hillenbrand, F. K.**: Lancet, **2**, 64, 1956. (37) **Hiro, Y.**, and **Tasaka, S.**: Monatschr. f. Kinderh., **76**, 328, 1938. (38) **Humphrey, T. F.**, and **Ekermeyer, E. E.**: Ohio State Med. J., **33**, 406, 1937. (39) **Ingalls, T. H.**: (a) New England J. Med., **243**, 67, 1950; (b) Ibid., **255**, 629, 1956; (c) A.M.A. Am. J. Dis. Child., **93**, 555, 1957; (d) Unpublished data. (40) **Ingalls, T. H.**, and **Purshottam, N.**: New England J. Med., **249**, 454, 1953. (41) **Ivstam, B.**: Acta oto-laryng., **39**, 380, 1951. (42) **Jackson, A. D. M.**, and **Fisch, L.**: Lancet, **2**, 1241, 1958. (43) **Johnson, R. E.**, and **Hall, A. P.**: New England J. Med., **258**, 743, 1958. (44) **Jonsson, V.**: Personal communication, 1959. (45) **Kelemen, G.**, and **Gotlib, B. N.**: Laryngoscope, **69**, 385, 1959. (46) **Korns, A. F.**: J. Inf. Dis., **90**, 183, 1952. (47) **Krugman, S.**, and **Ward, R.**: New England J. Med., **259**, 16, 1958. (48) **Krugman, S., Ward, R., Jacobs, K. G.**, and **Lazar, M.**: J. Am. Med. Assn., **151**, 258, 1953. (49) **Lancaster, H. O.**: (a) Brit. Med. J., **2**, 1429, 1951; (b) Acta Genetica et Statistica Medica. **5**, 12, 1954. (50) **Lancaster, H. O.**, and **Pickering, H.**: New Zealand Med. J., **51**, 184, 1952. (51) **Lewis, G. W.**: Rheumatism, **10**, 66, 1954. (52) **Loudon, I. S. L.**: Brit. Med. J., **1**, 1388, 1953. (53) **Lundström, R.**, and **Boström, I. L.**: Acta Ophthalmologica, **36**, 782, 1958. (54) **Mann, L.**: Tr. Ophth. Soc. Australia, **4**, 115, 1944. (55) Massachusetts Department of Public Health. Division of Communicable Diseases, Boston, Massachusetts. (56) **Maxcy, K. F.**: Rosenau's Preventive Medicine and Hygiene, New York: Appleton-Century-Crofts, 1956. (57) Metropolitan Life Insurance Company Statistical Bulletin, **40**, 1, 1959. (58) **Michael, M.**: Arch. Pediat., **25**, 598, 1908. (59) **Mills, C. A.**: Medical Climatology. Springfield: Charles C Thomas, 1939. (60) **Mitchell, W.**, and **Pampiglione, G.**: Lancet, **2**, 1250, 1954. (61) **Murray, N. E.**: Med. J. Australia, **1**, 126. 1949. (62) Official History of the Canadian Medical Services, 1939-45. Edited by **Feasby, W. R.** Ottawa: Queen's Printer, vol. **2**, chap. 35, p. 519, 1953. (63) **Oxorn, H.**: Am. J. Obst. & Gynec., **77**, 628, 1959. (64) **Papp, C.**: (a) Rev. d'Immunologie, **18**, 380, 1954; (b) Arch. Francaises de Pediatrie, **14**, 1053, 1957. (65) **Paterson, R.**: Edinburgh Med. and Surg. J., **53**, 381, 1840. (66) **Philbrook, F. R.**: Personal communication, 1959. (67) **Pickles, W. N.**: Lancet, **2**, 1046. 1956. (68) **Price, F. W.**: A Textbook of the Practice of Medicine. London: Oxford University Press. 1946. (69) **Rake, G.**: Rubella, in Viral and Rickettsial Infections of Man, edited by **Rivers, T. M.**, and **Horsfall, F. L.** Philadelphia: J. B. Lippincott Co., 1959. (70) **Reagan, R. L., Strand, N.**, and **Bruckner, A. L.**: Texas Rep. Biol. & Med., **2**, 507, 1953. (71) **Ritchken, I.**: Centr. Afr. J. Med., **2**, 85, 1956. (72) **Rusti, I.**: Rev. d'Immunologie, **21**, 393, 1957. (73) **Rutstein, D. D., Nickerson, R. J.**, and **Heald, F. P.**: A.M.A. Am. J. Dis. Child., **84**, 199, 1952. (74) **Sandberg, H.**, and **Simmons, I. H.**: U.S. Armed Forces Med. J., **4**, 1434, 1953. (75) **Schneider, B.**, and **Tottori, H.**: Unpublished thesis, Tulane University School of Medicine, 1959. (76) **Steen, E.**, and **Torp, K. H.**: Arch. Dis. Child., **31**, 470,

1956. (77) **Stokes, J., Jr.:** Rubella, chapter 8 in Preventive Medicine in World War II, Washington: Government Printing Office, vol. 4, 1958. (78) **Stuckey, E.:** Brit. Heart J., **18,** 519, 1956. (79) **Swan, C.:** (a) Medical Annual, **65,** 303, 1947; (b) Lancet, **1,** 744, 1948. (80) **Swan, C.,** and **Tostevin, A. L.:** Med. J. Australia, **1,** 645, 1946. (81) **Swan, C., Tostevin, A. L.,** and **Black, G. H. B.:** Ibid., **2,** 889, 1946. (82) **Swan, C., Tostevin, A. L., Moore, B., Mayo, H.,** and **Black, G. H. B.:** Ibid., **2,** 201, 1943.

(83) **Tadzer, I. S.:** Acta Med. Iugoslavia, **12,** 233, 1958. (84) **Tondury, G.:** Helvet. Paediat. Acta **7,** 103, 1952.

(85) **Wesselhoeft, C.:** New England J. Med., **236,** 943, 1947. (86) **Wildman, W. W.,** and **Teasey, W. B.:** Brit. Med. J., **1,** 851, 1940.

UNIVERSITY OF MICHIGAN LIBRARIES

BOOK REVIEWS AND NOTICES

THE BEGINNINGS OF EMBRYONIC DEVELOPMENT. A symposium organized by the Section on Zoological Sciences of the American Association for the Advancement of Science. Edited by ALBERT TYLER, California Institute of Technology; R. C. VON BORSTEL, Oak Ridge National Laboratory; and CHARLES B. METZ, Oceanographic Institute, The Florida State University. Pp. 400; 111 ills. Washington, D.C.: American Association for the Advancement of Science, 1957. Price, $8.75 (to A.A.A.S. members, $7.50).

THIS very informative volume is a collection of 13 articles, each with a different authorship, which deal with various aspects of the problems related to early development including differentiation and development of the oocyte, the initiation of development (substances and conditions influencing the entrance of the sperm into the egg), and nuclear and cytoplasmic factors related to subsequent events. Studies on a wide range of animal forms are reported and discussed. Each article gives an extensive review of the literature pertinent to the specific subject matter as well as reports of the author's own work. An extensive bibliography amounting to 1029 titles is made available if one adds up the lists of references included with each paper. A very worthwhile summarization of a large number of studies is presented and analyzed in this book. J.H.

DIABETIC MANUAL. BY E. P. JOSLIN, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School. 10th ed.; Pp. 304; 67 ills. Philadelphia: Lea & Febiger, 1959. Price, $3.75.

ADVANCES in the methods for the care of diabetic patients have come so rapidly that a new edition of this well-known manual is most timely. The author has done more to stimulate and inspire patients and physicians alike in the aggressive and vigilant management of this disease than any other person. His dictums concerning regularity and moderation in eating, exercise, rest, mental attitudes and daily living habits would serve well for the general public while, in truth, they provide a model of behavior for every diabetic patient. The manual will inform one of the history of diabetes, the basic physiology and biochemistry involved in the disease, and will promote the understanding of insulin, its actions and usage. The prevention and treatment of acute and chronic complications occupy large and important sections of this outstanding work. New additions in this 10th edition include the use of oral antidiabetic drugs and a chapter on the popular Food Exchange System of dietary treatment. It is a book that each diabetic patient, physician and student should digest thoroughly. C.S.

GRUNDRISS DER BAKTERIOLOGIE UND SEROLOGIE FÜR MEDIZINISCH-TECHNISCHE ASSISTENTINNEN. BY DR. HANS HEINRICH. 3rd ed. Pp. 134; 57 ills., many in color. Jena: Gustav Fischer Verlag, 1959. Price, DM 18.70.

THIS simple text has much to recommend it, as is evident from the fact that there have been three editions in 5 years. Outstanding are some of the colored photographs of bacterial colonies and stained smears. Following a very brief description of the nature of bacteria and of immunology, bacteria, rickettsiae, viruses, and fungi are systemically described. The approach in each instance is a brief statement of the pathogenic significance of the organism, its location in the patient, methods for examining clinical material, making cultures and identifying the isolate.

There are shortcomings in all outlines of this type, usually of omission, and this is no exception. The techniques are not all presented in enough detail to carry the technician through the many pitfalls encountered in their performance. A case in point is the serologic tests for syphilis. Nor could this reviewer find any mention of the treponemal antigens now being employed in syphilis serology.

The technical section contains useful information on bacterial stains, culture media, and antibiotic susceptibility testing, although the procedures selected are often different from those generally used in America. This specialized text is better than most English counterparts of similar size and as good as some others twice as large. E.S.

THAT THE PATIENT MAY KNOW. BY HARRY F. DOWLING, M.D., Sc.D., and TOM JONES, B.F.A., University of Illinois. Pp. 139; 90 ills. Philadelphia and London: W. B. Saunders Company, 1959. Price, $7.50.

THIS is a schematic anatomical atlas covering the major organ systems and the more common disorders affecting them. Its purpose is to aid the physician in his explanations to patients.

Each disorder is described by a plate with labels indicating function and malfunction. While some of the plates are a bit detailed they are, on the whole, simple enough to facilitate the patients' understanding of their illnesses.

This atlas should be of value to the physician whose patients require explanations in addition to good medical care. W.S.

MICROBIOLOGY YESTERDAY AND TODAY. Edited by VERNON BRYSON, Institute of Microbiology, Rutgers University. Pp. 122; 28 figures and tables. New Brunswick, New Jersey: Institute of Microbiology, 1959. Price, $4.00.

THE proceedings of a one-day symposium in June, 1958, are contained in this small book. As a tribute to Dr. Selman Waksman, the subjects discussed are those with which this microbiologist has been most energetically concerned during his scientific career. Each of the 7 papers is a historical review which omits detailed description of individual experiments, and this reviewer found them all interesting, informative, and a delight to read. The authors are all eminently qualified by training. Microbial biochemistry, for example, is discussed by Quastel, antibiotics by Woodruff, immunochemistry by Heidelberger, bacterial taxonomy by Cowan of London, and microbial genetics by Bryson. The last two papers are of a different nature. Skriabin of the U.S.S.R. takes an unnecessarily defensive attitude in outlining the past achievements and present vigor of Russian researchers in microbiology. The final discussion is by Waksman, who ends it with a warning against the prevalence of overspecialized training in microbiology. Young biologists who take the time to read this short volume will gain perspective and be rewarded with many a sage comment about research, scientific education, and the role of microbiology in the human economy. E.S.

HANDBOOK OF DIET THERAPY. By DOROTHEA TURNER, Department of Medicine, University of Chicago. 3rd ed. Pp. 222. Chicago: The University of Chicago Press, 1959. Price, $5.00.

THE new revision of this authoritative work advances admirably the objective of improving the level of teaching the essentials of nutrition and of adapting these principles in the treatment of disease states. The initial section contains the basic normal dietary plan, its modification for various physiological events and correlations with Recommended Dietary Allowances. The chapters dealing with therapeutic diets establish a further series of modifications of the basic dietary pattern devised to maintain or improve nutritive efficiency in the presence of many specific diseases. An analysis of the fat and fatty acid content of the diet is presented with values of saturated and unsaturated fatty acids and cholesterol in various food groups and a sample meal plan for a suitable low-fat diet. A new addition is that of the management of phenylketonuria and intestinal malabsorption syndromes achieved by means of modifications of protein intake. The section entitled "Interviewing the Patient" by Margaret Mead reflects the current need for considering the patient as a whole personality, especially in dealing with problems in nutrition and dietetics. The appendices include evaluations of nutritive values of foods and other data for the use of dietitians and physicians; these tables are complete and well-organized. C.S.

TREATMENT OF LUNG CAVITIES AND ENDOBRONCHIAL TUBERCULOSIS WITH SPECIAL REFERENCE TO TREATMENT IN MALAYA. By BERYL E. BARSBY, M.D., M.R.C.P., General Hospital, Johore Bahru, Malaya. Pp. 147; 46 ills. Edinburgh and London: E. & S. Livingstone, Ltd. (The Williams & Wilkins Co., Baltimore, exclusive U.S. agents), 1959. Price, $4.75.

THE author performed more than 1100 bronchoscopies, under general anesthesia, in patients with active pulmonary tuberculosis. One hundred cases were studied intensively before and during treatment. Biopsies were taken "whenever possible." The over-all incidence of tuberculous endobronchitis was 75%. Six grades of bronchial involvement are recognized, these bore no relationship to the radiologic type of disease. Recessive changes were well correlated with the type and duration of treatment.

The very important relationship between tuberculous cavitation and endobronchial disease is stressed. This is a "two-way street," bronchial involvement not only affects cavitation, but persistent cavitation, especially with bacillary sputum, tends to prevent healing of bronchial tuberculosis. The author presents interesting observations on "tension cavities,"

UNIVERSITY OF MICHIGAN LIBRARIES

with records of intracavitary pressures, and studies of the behavior of opaque contrast media. The very high intracavitary pressures (+30, +40 cm. H_2O) due to cough are felt to play a most important role in the production of tension cavities.

"Postural retention," the opposite to postural drainage, was employed in an effort to block the draining bronchus and to accelerate healing. The author is enthusiastic about the results of this procedure and considers it almost as important as drug therapy.

Short chapters are included on: Surgical Aspects of Tuberculosis in Malaya; The Management of Tuberculous Pyopneumothorax; Anesthesia for Bronchoscopy; and Physiotherapy of Tuberculous Lung Conditions in Malaya. Except for the description of anesthesia, which might make many bronchoscopists shudder, these are not germane to the main subject of the book. Typography and illustrations are good, references plentiful, index included.

One might quarrel with some of Dr. Barsby's conclusions, or quibble over details of patient-management. However, two conclusions are inescapable. First, the importance of the endobronchial component of pulmonary tuberculosis is properly stressed. Perhaps even more important, this volume is a splendid example of excellent clinical research, diagnostic and therapeutic, carried out by devoted and enthusiastic physicians under extremely difficult conditions. R.C.

JACOPO BERENGARIO DA CARPI (CA 1460–1530). A SHORT INTRODUCTION TO ANATOMY (ISAGOGAE BREVES). Translated with an Introduction and Historical Notes by L. R. LIND and with Anatomical Notes by PAUL G. ROOFE. Pp. 228; 22 ills. Chicago: University of Chicago Press (Cambridge University and University of Toronto Presses), 1959. Price, $5.00.

BERENGARIO DA CARPI is important in the history of anatomy both because of his own contributions and because his two chief works, the earlier "Commentary on Mondinus," and this "Short Introduction to Anatomy," form a good bridge between the medieval period and the medical Renaissance (Versalius' Fabrica). This translation (the second in English, the first by Henry Jackson, 1660 being practically unobtainable) was suggested to Dr. Lind by Dr. H. W. Magoun of Los Angeles. It appears to have been carried out in the thorough, reliable way that was to be expected from this distinguished scholar. The many obstacles to his progress are illustrated in the first paragraph of the Introduction, by the numerous names that have been used for this Italian author. It is easy to see why an English translation of his most important work, the "Commentary" has never yet been attempted; let us hope that Dr. Lind, familiarized with the situation by his labors on the "Introduction," may some day undertake the larger job.

Parenthetically, the 26 pages of the Introduction will doubtless afford the greatest interest to most. For the professional anatomists with historical leanings, the translator's notes and the anatomical notes by Dr. Roofe will be the Ariadne's thread through the mazes of the labyrinth. Like all the anatomical treatises of this period, the complexities of Berengario's methods (incidentally mixing a descriptive anatomy with a dissecting manual), his strange nomenclature, and inaccurate illustrations that have but the one merit of vigor, all tend to make the necessarily difficult reading still more difficult. But all the more credit must go to the two University of Kansas scholars for their successful achievement.

Opinions about Berengario's powerful and successful figure are mostly far from favorable: N. Putti, one of his most reliable biographers (1937), allowed that he was more stirred by avarice and cupidity than by ambition and virtue; Dr. Lind emphasizes (giving examples) his rapacity, greed, malice and ruthlessness, though accepting his successful qualities in teaching—even including some experimental studies—and in amassing a large and lucrative practice. Two supposed portraits are mentioned by Lind, but neither is authentic (Putti).

Congratulations on a well performed and valuable contribution to American medical scholarship! E.K.

THYROID RADIOIODINE UPTAKE MEASUREMENT. A STANDARD SYSTEM FOR UNIVERSAL INTERCALIBRATION. United States Atomic Energy Commission Technical Information Service. Pp. 323; illustrated. Washington: Office of Technical Services, Department of Commerce, 1959. Price, $3.50.

BRUCER and The Oak Ridge Institute of Nuclear Studies have undertaken an extensive series of investigations on the accuracy of various uptake systems, both here and abroad. The multitude of errors which can enter into the determination of thyroidal uptake of radioactive iodine are engagingly discussed, and dramatically and often humor-

ously and bitterly presented. On the basis of his investigations, the author has arrived at an ideal uptake measuring system. Those who have done much experimental work on their own uptake systems will be qualified to disagree with the recommendation of this particular method of doing thyroidal uptakes, but those who have not undertaken such experimental checking of their systems will not be qualified to defend their own particular uptake system against the accusations of carelessness and poor physical foundation made by Brucer in this most interestingly written examination of the factors entering into accuracy of thyroid uptake measurements. It is therefore highly recommended reading for all doing thyroid uptakes. R.R.

PREVENTIVE MEDICINE: PRINCIPLES OF PREVENTION IN THE OCCURRENCE AND PROGRESSION OF DISEASE. Edited by HERMAN E. HILLEBOE, M.D., Commissioner of Health, and GRANVILLE W. LARIMORE, M.D., Deputy Commissioner of Health, State of New York, Department of Health, Albany. Pp. 731; 59 ills. Philadelphia: W. B. Saunders Co., 1959. Price, $12.00.

THIS volume is a welcome addition to the field of preventive medicine, a science closely allied to curative services in everyday practice. It provides an up-to-date text for medical students, general practitioners, specialists and other workers in health agencies. Written in fluent style by 31 experts in various disciplines, it will be useful too for dental, nursing, pharmacy and osteopathy students, and for the interested general reader.

Topics covered in the book's 41 chapters relate to the prevention of disease and limitation of progression should disease appear, in the individual and the group. This modern point of view, an optimistic and practical one, is unfortunately at times more ideal than real in application. A knowledge of prevention of illness and accidents is obviously desirable for all.

The first part of this book, prevention of occurrence, is the key section. It includes environmental sanitation, prophylaxis of disease, nutrition, maternal and child health and preventive dentistry. The second part, prevention of progression, covers periodic health inventories, early detection and follow-up, rehabilitation and addictive disorders. Part three, supportive services, reviews health education of the public and professional training, social work, public health nursing, epidemiology, the role of the hospital, official and voluntary health agencies. The latter two parts pertain to limiting diseases as they occur and limiting disability, public health activities more applicable to groups than individual patients.

Technically attractive and sturdily bound this book is a valuable contribution to a promising medical specialty. F.R.

DIE MITOGENETISCHE STRAHLUNG. BY A. G. GURWITSCH AND L. D. GURWITSCH (Moskau) (Translated from the Russian). Pp. 308; 50 ills. Jena: Gustav Fischer Verlag, 1959. Price, DM 27.65.

A BOOK on the controversial problem of mitogenetic radiation written by the deceased originators of the discipline and brought up-to-date by a group of co-workers and disciples certainly is of some lasting interest. For scientists, not conversant with the Russian language, the German edition makes the results of the very large pertinent Russian literature accessible. Without going into details, it seems of interest that the authors concede that it was impossible for them to bring their results and the classical theory to some kind of agreement. They limit themselves to attempt an analysis of the causal role of the mitogenetic radiation in normal and malignant cell division and they try to analyze these changes. The German translation is readable. M.S.-A.

PROCEEDINGS OF CONFERENCE ON "MAN VERSUS ENVIRONMENT" May 5-6, 1958. Sponsored by the National Institutes of Health and Bureau of State Services, U.S. Public Health Service. Edited by HARRY A. FABER, Division of Sanitary Engineering Services, U.S. Public Health Service. Pp. 143. Washington: U.S. Public Health Service, 1959.

THIS publication, summary of a two-day conference by experts in environmental health, provides a comprehensive look at the present complex entourage of man. Eighty-five participants contributed papers and group discussion about water supply, water pollution, air pollution, food technology, and occupational health. Problems resulting from technical progress, research and training needs, and areas of recent activity are tersely summarized in these well-edited minutes.

In a Keynote Address, "Human Health and the Modern Environment," Dr. Robert A. Kehoe, citing occupational and public health problems in today's industrial society, con-

UNIVERSITY OF MICHIGAN LIBRARIES

cludes with optimism: "It is clear that reckless man can turn loose and build up physical forces which may destroy himself and his kind. It seems probable, however, that the same ingenuity which thus far has enabled him to explore and penetrate other secrets of nature will serve his need when expended in learning more about his own vulnerability and in developing means for self-protection."

These proceedings are recommended for all who are interested in the contemporary challenges related to man and his environment. F.R.

THE TRUTH ABOUT YOUR EYES. By DERRICK VAIL, M.D., Northwestern University Medical School. 2nd ed. Pp. 173; 6 ills. New York: Farrar, Straus & Cudahy, 1959. Price, $3.50.

THIS is a book that fills an important void. There are few books written for the intelligent patient who wants a more detailed explanation about some eye problem. This is a book you can leave in your waiting room or loan to a patient without anticipating that it will raise more questions than it will answer. The topics are briefly and adequately discussed. I would recommend it as a worthwhile addition to any ophthalmic library and suggest that it be left in a place where the patients have access to it. L.H.

NOTES OF A SOVIET DOCTOR. By G. S. PONDOEV, M.D. Pp. 238. New York: Consultants Bureau, Inc., 1959. Price, $4.95.

THE author, an elderly, experienced, erudite and respected practitioner, attempts in this book to honor his country and Soviet medicine by recounting the contributions and advances made by men dedicated to communist ideologies. Although the contributions of Harvey, Darwin and Bernard are appreciated by Pondoev, it is obvious that he believes the "new and better" Soviet Doctor was born from the labors of Marx and Lenin.

This reviewer, having just returned from a visit to the Soviet Union, could almost anticipate the ideological double-talk that the author propounds. He would have us believe that the "compleat" Soviet physician can owe his first allegiance to the state, the community and the individual all at the same time. In similar fashion he deplores the Western concept of the "Art" of medicine as being materialistic but states, "for success in treatment, besides knowledge it is essential to have a certain 'something' which is what every patient seeks in the doctor, and is why he calls him 'his doctor'."

Not content with an enumeration of the contributions of such men as Pavlov, Mechnikov, Orveli and others, the author, in provincial chauvinistic fashion, claims that it was Perogov and not Florence Nightingale who introduced the "sisters of mercy" and that two of Botkin's students anticipated the discovery of penicillin in 1871.

The author's claim of the "undoubted superiority of the Soviet doctor over the doctor in capitalist countries" was not substantiated by my visit to the U.S.S.R. nor is this reviewer impressed by references to neuralgia of the solar plexus, the scientific advances of spa treatment and balneotherapy and the value of antireligious propaganda in prophylaxis of disease.

This text will be of interest to those who wish to understand the present-day Soviet doctor. S.L.

CANCER IN FAMILIES. By DOUGLAS P. MURPHY, M.D., Emeritus Professor of Obstetrics and Gynecology, School of Medicine, University of Pennsylvania and HELEN ABBEY, Sc.D., Assistant Professor of Biostatistics, School of Hygiene and Public Health, The Johns Hopkins University. Pp. 74. Cambridge, Mass.: Harvard University Press for The Commonwealth Fund, 1959. Price, $2.50.

THIS little book represents the detailed reporting of a well-controlled study concerning hereditary factors in breast cancer. This study in many respects is similar to other studies, such as the one by Jacobsen, in 1946, and others. The reason for performing this study was that the authors felt there were several areas of error that had crept into other studies and they wished to eliminate them. This is a retrospective study, however.

The conclusions are: 1) If the familial tendency to develop cancer did exist, it was not large enough to be detected in a study of this size. R.T.

SYNOPSIS OF EAR, NOSE, AND THROAT DISEASES. By ROBERT E. RYAN, B.S., M.D., M.S.(ALR), F.A.C.S., Department of Otolaryngology, St. Louis University School of Medicine; WILLIAM C. THORNELL, A.B., B.M., M.D., M.S.(ALR), F.A.C.S., Assistant Professor of Otolaryngology, Cincinnati College of Medicine, and HANS VON LEDEN, M.D., F.A.C.S., F.I.C.S., Assistant Professor of Otolaryngology, Northwestern University Medical School; Associate Professor, Cook County Graduate School of Medicine. Pp. 383; 59 ills. St. Louis: C. V. Mosby Co., 1959. Price, $6.75.

This compact volume is a concise, systematic and up-to-date digest of the common ailments involving the ears, nose and paranasal sinuses, pharynx and larynx. It includes the essentials of anatomy and physiology and brief descriptions of the usual techniques and tests employed in routine examinations. The common diseases are discussed in relation to etiology, pathology, prognosis and treatment with the symptoms and treatment repeated in outline form at the end of each chapter. Brevity and clarity have been achieved by omitting variations in accepted treatment and by including only those surgical procedures of interest to the family physician, intern and medical student. The text is well illustrated but bibliographic references have been dispensed with as nonessential for the purposes of the volume. As the authors point out, the synopsis is not comprehensive enough for the resident or specialist in otolaryngology. However, it can be highly recommended as an exceptionally useful and sound source of information for general practitioners, interns, medical students, nurses and speech or voice pathologists. H.S.

The Annual Survey of Psychoanalysis, Volume V. Edited by John Frosch, M.D. and Nathaniel Ross, M.D. Pp. 608. New York: International Universities Press, Inc., 1959. Price, $12.00.

The editors, editorial board and contributing editors are to be congratulated on this important reference book. This fifth volume, covering the 1954 literature, is distinguished for the excellency of the abstracts, sometimes more readable than the original article. As in the previous volumes, the logical grouping of the articles, adds meaning to the book as a survey of psychoanalysis. The editorial introductions to some of the chapters contribute to the importance of this volume.

The survey includes reviews of ten pyschoanalytic books. There is a complete bibliography, a detailed table of contents and index. The Annual Survey of Psychoanalysis will interest all psychoanalysts, psychiatrists and all interested in psychological medicine. M.B.

The Degenerative Back and Its Differential Diagnosis. By P. R. M. J. Hanraets, M.D., Neurosurgeon, St. Ursula Clinic, Wassenaar, The Netherlands. Translated by Miss M. E. Hollander, London. Pp. 690; 15 ills., 12 in color. Amsterdam: London: Princeton: Elsevier Publishing Co., 1959.

In the category of clear medical writing this text by Hanraets leaves much to be desired. The sentences are involved, the text disorganized, and the graphs difficult to interpret. There are some excellent illustrations and color photographs of pathologic entities, but the entire 653 pages could have been reduced to a small monograph the size of his 10 page summary and conclusion and have lost very little in the telling. The author's operation around which the whole text seems to be built is far too radical and extensive for the nonspecific complaints for which it is designed.

The author is in many points at issue with current American medical thinking, and his terminology is involved and unfamiliar; perhaps it has suffered in translation.

The book could be recommended to a very careful, patient, mature reader interested in Dr. Hanraets' experience. H.S.

Third Tissue Homotransplantation Conference. By John Marquis Converse and Blair O. Rogers, Conference Co-Chairmen, Institute of Reconstructive Plastic Surgery, New York University-Bellevue Medical Center and the Department of Surgery, New York University College of Medicine, New York, N.Y. Third Conference. Pp. 327; 171 ills. New York: The New York Academy of Sciences, 1958.

This is a monograph representing the collective papers, based on the third biennial Tissue Homotransplantation Conference. The contributors are international. The monograph is divided into four parts with a total of approximately 37 presentations. These papers demonstrate the rapid advances made in this field and indicate the approaches that have been taken and that have been opened up in this science of tissue transplantation. One of the interesting subjects discussed in this monograph is a group of papers relative to antibodies and antigens in tissue transplantation. This is a valuable text for the plastic surgeon and for those interested in the research development of this relatively new scientific field. A.P.

Health in Industry. By Donald Hunter, M.D., F.R.C.P. Senior Physician to and Director of Research in Industrial Medicine at the London Hospital. Pp. 288; 8 ills. Baltimore: Penguin Books, Inc., 1959. Price, $0.95.

This book, a concise account of industrial health and diseases, is written by an eminent authority in the field. An earlier volume by Dr. Hunter, *The Diseases of Occupations*, 1957, was comprehensive and well received. The author's introduction to the problems of health in industry came in 1925 when he worked with Dr. Joseph C. Aub at Harvard on lead poisoning.

UNIVERSITY OF MICHIGAN LIBRARIES

Since that time he has had an extensive experience in industrial medicine.

The present work emphasizes the fact that prevention is better than cure in industrial practice. Architects, chemists, engineers, public health and private physicians all cooperate to achieve this goal. The role of agencies concerned with health problems in industry is examined, and chapters deal with such topics as accidents, poisoning, dust diseases of the lungs, occupational hazards and modern labor legislation.

A glossary of technical terms for the general reader and a useful bibliography complete this readable book. F.R.

Quistes Hidatidicos del Nigade Abiertos en Vias Biliares (Hydatid Cysts of the Liver with Rupture into the Biliary Tract.) By Pedro L. Cereseto. Pp. 135; 56 ills. Buenos Aires, Argentina: Lopez & Etchegoyen, 1958.

This book deals with the diagnosis and treatment of this complication of hydatid cysts. It contains an extensive review of the literature and report of 7 cases. F.C.

The Birth of Normal Babies. By Lyon P. Strean, Ph.D., D.D.S., F.A.P.H.A., Consultant, Norristown State Hospital, Norristown, Pa. Pp. 194. New York: Twayne Publishers, Inc., 1958. Price, $3.95.

According to the author, congenital anomalies are a result of excessive cortisone secretion following unusual emotional or physical stress during early pregnancy. He presents numerous case histories of pregnancies which terminated in the birth of abnormal infants which are presumed to prove his thesis. Many of the accidents were of the same minor types which occur almost daily to everyone. No controls are included and he fails to mention the many reported instances in which individual patients or groups of patients have been treated with cortisone throughout pregnancy without effects on fetal development.

Although it is quite possible that certain stressful situations might disturb the normal orderly course of fetal development, this book does not help to answer the question. In fact it sounds much like the volumes concerning the effect of "maternal impressions" which were so prevalent 50 years ago. It contains little information of value to physicians and would only cause expectant mothers to worry because any minor scratch, bump or infection might "mark" her baby. J.W.

The Journal of the Human Factors Society of America, Vol. 1, No. 1. New York: Pergamon Press, September, 1958. Price, Journal: $10.00 per year subscription; Bulletin: $5.00 per year subscription.

This is Volume 1, Number 1 of The Journal of the Human Factors Society of America. It is chiefly concerned with man-machine relationships and the increased efficiency of such relationships. Those working in this field are chiefly psychologists and engineers and the language of the journal reflects this. Its interest would seem limited to physicians in Industrial Medicine. W.S.

Hospital Happy. By Evelyn Barkins. Illustrated by Louis Di Valentin. Pp. 109; 50 ills. New York: Frederick Fell, Inc., 1959. Price, $1.98.

Some gay and witty verses to amuse and while away the tedium of those who, by necessity or occupation, have to do with hospitals. R.K.

The Sedimentation Rate of Human Erythrocytes. By Frank Wright, M.D. Pp. 43; 4 ills. New York: Vantage Press, Inc., 1958. Price, $2.50.

In this small volume, the author undertakes an interpretation of the basic aspects of the erythrocyte sedimentation phenomenon, its value as a differential diagnostic agent, and its multiple clinical applications. Of the many who have championed the sedimentation rate, few have attributed such sweeping significance to it as the writer. His principal view is indicated by his suggestion that the sedimentation rate may be used to measure "energy at work," and that the test has "not only great value but possibilities as yet unheard of." Indeed, he goes so far as to propose that the test be used "specifically as a measure of damage caused by atomic fallouts" in the population at large. C.Z.

Dorland's Pocket Medical Dictionary. Abridged from Dorland's Illustrated Medical Dictionary. 20th ed. Philadelphia: W. B. Saunders Co., 1959. Price, $4.50.

The profession will welcome this the 20th edition of a work that has become a standard on the desk of the physician and of his secretary. R.K.

British Medical Bulletin, Vol. 15, No. 1, January, 1959. Pp. 84; illustrated. London: Medical Department, British Council, London, 1959. Price, $3.25.

This issue is devoted to a timely review of important progress in the field of Hematology. The articles are written concisely and clearly by leading British authorities, and may be recommended to all who wish to keep abreast the developments in this rapidly growing area. C.Z.

Year Book of Drug Therapy (1958–1959 Year Book Series). Edited by Harry Beckman, M.D., Departments of Pharmacology, Marquette University Schools of Dentistry and Medicine. Pp. 569; illustrated. Chicago: Year Book Publishers, Inc., 1959. Price, $7.50.

THIS volume presents the essential therapeutic elements culled from some 493 articles which appeared during the past "series year." As with its predecessors, the author has done an excellent job in surveying recent progress in drug therapy. All clinicians will find this a helpful reference to new forms of treatment, to expected responses and to possible untoward effects from their use. C.Z.

Polysaccharides in Biology. Transactions of the Third Conference, May 29, 30 and 31, 1957. Edited by GEORG F. SPRINGER, M.D., University of Pennsylvania. Pp. 249; 58 ills. New York: Josiah Macy, Jr. Foundation, 1958. Price, $4.75.

THIS volume consists of the transactions of the Third Conference on Polysaccharides in Biology, which was held at Princeton, N.J. in May, 1957. The major topics were: Homopolysaccharides discussed by DeWitt Stetten, Jr. and Marjorie R. Stetten; and Nucleotides and Saccharide Synthesis, by Luis F. Leloir. Both the presentations and the intragroup discussions will be of interest to all research workers who are concerned with biological processes involving these and related substances. C.Z.

Medical Education. Annotated Bibliography, 1946–1955. Pp. 391. Geneva: World Health Organization, 1958. Price, $6.75.

THE World Health Organization has performed a signal service in collecting this bibliography on all phases of medical education. Administrators of medical schools and members of their faculties will find here a most helpful guide to pertinent information and opinions. R.K.

Thrills and Regressions. BY MICHAEL BALINT, M.D., Member of the Faculty of the British Psychoanalytic Society and Institute. Pp. 148. New York: International Universities Press, Inc., 1959. Price, $4.00.

THIS volume deals with primitive attitudes toward the world surrounding us. Two types are described. The first, the Oenophil, clings to objects and lives in the illusion that as long as he is in touch with a safe object he himself is safe. The second, the philobat wishes to be free from ties and lives in the illusion that apart from his own proper equipment he needs no objects.

The book gives the impression of being rather subjective, and no clinical material is presented. It is not clear how the author arrives at his conclusions. M.B.

Conceptual and Methodological Problems in Psychoanalysis. BY LEOPOLD BELLAK, M. OSTOW, E. PUMPIAN-MINDLIN, A. H. STANTON, AND T. S. SZASZ. Pp. 163. New York: New York Academy of Sciences, 1959. Price, $2.75.

THE purpose of the book is to examine critically some of the basic concepts of psychoanalysis and, wherever necessary, suggest a revision that will make them still more useful for practice and theory. The major part of the book deals with an attempt at a systematic restatement of the libido theory. The concepts of libidinal zones, object choice, and the energetic economic aspects of the libido theory are discussed.

This is a valuable volume for everyone interested in psychoanalysis. M.B.

La Médecine Légale Judiciaire. BY JEAN PLANQUES. Pp. 127. Paris: Presses Universitaires de France, 1959.

THE essentials of legal medicine as they obtain in France set forth in a series of brief presentations on manifold subjects for lay consumption, published by the University Presses of France.

Opiates and Opiate Antagonists. BY ABRAHAM WIKLER, M.D. Pp. 33. Washington: U.S. Public Health Service, 1959.

Hodgkin's Disease. BY ANTONIO ROTTINO AND 33 OTHERS. (Ann. New York Acad. Sci., 73, Art. 1, 1958.) Pp. 380; illustrated. New York: New York Acad. Sciences, 1958.

The Chemistry of Blood Coagulation. BY PAUL MORAWITZ. Translated by ROBERT C. HARTMANN, M.D., AND PAUL F. GUENTHER, M.A., PH.D., Vanderbilt University. Pp. 194; 1 ill. Springfield, Ill.: Charles C Thomas, 1958. Price, $4.50.

THIS is an excellent English translation of "Die Chemie der Blutgerinnung" which was originally published in 1905. It provides the historical background for the so-called classical theory of blood coagulation which was promulgated over 50 years ago by Morawitz, Fuld and Spiro. While students of the clotting mechanism will be particularly interested in this monograph, it is commended to all physicians as a fine example of the important relationship of historical perspective to current investigational activities in a given field. C.Z.

La Chinidina in Terapia. BY C. BONESSA AND M. MORPURGO, Dall Instituto di Idrologia Medica dell' Universita e dall' Ospedale Policlinico di Milano. Pp. 122; 28 ills. Torino: Minerva Medica, 1958.

THIS is a monograph, written in Italian, which reviews the pharmacology of quinidine, especially as applied therapeutically to man, and offers, in addition, some of the authors' own results and experiences. It should interest most cardiologists, particularly if they read Italian or can have

UNIVERSITY OF MICHIGAN LIBRARIES

the monograph accurately translated. Of particular interest is the conclusion by the authors that the negative inotropic effect (depression of contractile force) has been greatly overemphasized, especially as the drug is used in man therapeutically. They offer reasonably good data, obtained in Mansby cardiac catheterization techniques, by themselves and others to support this conclusion. R.S.

Principles of Administration Applied to Nursing Service. By H. A. Goddard, Goddard & Company, Management Consultants, London, England. Pp. 108. Geneva: World Health Organization, 1958. Price, $4.00.

Heredity Counseling. Edited by Helen G. Hammons, Managing Editor, Eugenics Quarterly. Pp. 112; 1 ill. New York: Paul B. Hoeber, Inc., 1959. Price, $4.00.

This report of a Symposium sponsored by the American Eugenics Society consists of 17 short essays by leading experts. Discussed are some of the major practical relationships between advances in knowledge of heredity and the developing importance of skilled genetic counseling in problems of marriage and childbearing. To the comparatively uninformed medical reader this little volume can serve as an excellent description of the role and scope of this new medical specialty. I.W.

The Principles of Therapeutics. By J. Harold Burn, M.A., M.D., F.R.S., Professor of Pharmacology, University of Oxford. Pp. 278; 35 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $5.50.

This book contains the lectures on "Pharmacology and the Basis of Therapeutics," which are presented by the author to Oxford University medical students. The material is well-organized and the writing lucid. Practicing physicians as well as medical students will find this a valuable blend of pharmacology and therapeutics. C.Z.

Melanoblasts and Melanocytes in Fetal Negro Skin. By Arnold A. Zimmerman, and Samuel W. Becker, Jr., Departments of Anatomy and Dermatology, College of Medicine, University of Illinois. Pp. 59; 26 ills. Urbana, Ill.: University of Illinois Press, 1959. Price, $2.25.

This is a short and concise monograph on the development and population density of fetal melanoblasts and melanocytes in Negro skin based on thin horizontal sections of skin from one hundred six fetuses, varying in age from the seventh week to birth. It traces the origin of the melanin-producing cell from the neural crest to the dermis and eventually into the epidermis. A.P.

Metabolic Factors in Cardiac Contractility. By Menard M. Gertler and G. W. E. Plaut and 18 Others. (Otto v. St. Whitelock, Editor-in-Chief, Annals of the New York Academy of Sciences). Pp. 171; illustrated. New York: New York Academy of Sciences, 1959. Price, $3.75.

This volume maintains the high standards set by the New York Academy. The authors are all recognized in their particular interests. Numerous pictures, diagrams and illustrations are included. While all sections are good, particularly to be recommended are: Utter on "Carbon Dioxide Fixation" and Overman on "Physiological Effects of Ions." The publication serves to focus attention on our newer knowledge of cellular cardiac physiology. M.O.

Overfed but Undernourished, Nutritional Aspects of Health and Disease. By H. Curtis Wood, Jr., M.D., Associate in Obstetrics, Episcopal Hospital, Philadelphia. Pp. 95; 1 ill. New York: Exposition Press, 1959. Price, $2.50.

The relationship between various diseases and nutrition is examined superficially and without supporting scientific data in this book. While the objective of the book in promoting improvement in dietary patterns is laudable, no purpose is served by the inclusion of untested impressions and hypotheses. The lay public for whom the monograph is obviously intended is incapable of evaluating the material contained in it, much of which is of questionable accuracy. In the book, vitamin C is recommended in prevention or treatment of cardiovascular disease, respiratory diseases, liver disease, kidney disease, nervous diseases; testimonials from patients are quoted recommending kelp tablets, multivitamins and food supplements of various types. The book is not recommended. C.S.

Pulmonary Circulation. Edited by W. R. Adams, M.D., and Ilsa Veith, Ph.D., Chicago Heart Association. Pp. 310; 126 ills., 1 in color. New York: Grune & Stratton, Inc., 1959. Price, $4.50.

An up-to-date presentation of our present concepts of the field of pulmonary circulation is included in this book. The participant authors are all well recognized and their presentations are authoritative. Both the physiology and pathology of the lung circulation are included. Not only are the dissertations well worth while but the discussions also include valuable material. The figures are informative and clear. This work can be recommended for graduate students, researchers in the field and internists in general.

The sections entitled "Effects of Lung Inflation on the Pulmonary Vascular Bed" and "Vascular Tree" are particularly stimulating in the part on Pathology. In the section on Physiology the paper "Instantaneous Pulmonary Capillary Blood Flow" constitutes in conjunction with that on "The Pulmonary Capillary Bed: Volume

Area and Diffusing Characteristics" a valuable group of concepts. M.O.

Your Mind Can Make You Sick or Well. By Curt S. Wachtel, M.D. Pp. 244. New York: Prentice-Hall Inc., 1959. Price, $4.95.

The purpose of this book is to indicate "how to let the wonderful powers of your mind bring you magnificent health and complete well-being." A life-chart is included to serve as a "magic mirror" to reflect the causes of your emotional problems.

The author purports to help people understand their minds and use their minds to keep their health or regain lost health. One typical illustration is the case of "Marlene." The author said to her, "since you admire a person who thinks his own thoughts, why don't you try to become that sort of a person?" Marlene re-educated herself to become that sort of a person and this resulted in cessation of her gallbladder colics.

This book may appeal to the naive layman. To the more sophisticated reader the book will be recognized for fiction rather than for any medical value. M.B.

Maternity: A Guide to Prospective Motherhood. By Frederick W. Goodrich, Jr., M.D. Illustrated by Victor Mays. Pp. 127; illustrated. New York: Prentice-Hall. Inc., 1959. Price, $1.75.

This refreshing little book, which is intended to introduce prospective mothers and fathers to the process of childbearing, is one of the best of the many that have been written in recent years. The author is obviously an understanding, as well as an articulate, obstetrician who has not only had considerable clinical experience but who has listened to and remembered his patients' questions and who understands their problems. Most of the things with which pregnant women should be familiar and those about which they are curious are discussed in a simple, dispassionate yet comprehensive and uncondescending manner.

A minimum of space is devoted to considerations of anatomy (2 pages), infant development (3½ pages) and similar subjects, and complications such as bleeding, the signs of toxemia, and the like, the dire consequences of which are often so graphically described, are mentioned as things which should be reported but are not over-emphasized. The material is well indexed and is divided into related sections which make the book an excellent one as a text for prenatal parent instruction. J.W.

How to Sleep Well. By Dr. Samuel W. Gutwirth, Educator in Scientific Relaxation. Pp. 97. New York: Vantage Press, Inc., 1959. Price, $2.95.

This book purports to teach the techniques of tension control. The purpose of scientific relaxation is to achieve natural rest and to promote the most efficient use of the human body. The book, following the lead of Dr. Edmund Jacobson, holds to the belief that it is impossible to be nervous in any part of the body if in that part the muscles are completely relaxed.

Most psychiatrists would believe that the author confuses cause and effect; tension, a symptom, is viewed as the illness. The book does discuss tension as an expression of psychic conflict. M.B.

Insulin Treatment in Psychiatry. Edited by Max Rinkel, M.D. and Harold E. Himwich, M.D. Pp. 386; 23 ills. New York: Philosophical Library, 1959. Price, $5.00.

This volume includes the papers presented at the 1958 International Conference on the Insulin Treatment in Psychiatry held at the New York Academy of Medicine. Distinguished proponents and opponents of the insulin shock treatment are represented in the list of authors and panel members.

The papers and discussions cover the historical contributions, physiochemical research, clinical research and follow-up studies on insulin treatment in psychiatry. The reader will find in this volume a comprehensive evaluation of the current status of insulin therapy. M.B.

Medical Science and Space Travel. By William A. Kinney. Pp. 150; 71 ills. New York: Franklin Watts, Inc., 1959. Price, $3.95.

In this small volume the dramatic steps which have been taken to bring man to the threshold of space travel have been vividly retold. The author, who is scientific editor of the official journal of the U.S. Air Force, "The Airman," has a wealth of experience and source material upon which to draw. As a result, the text is authentic and generously illustrated with photographs of Americans who have contributed to this challenging area, and of events which have proved to be landmarks of progress.

It is recommended to anyone interested in the flow of events which has led man to his present position in the count-down to space flight. C.Z.

Antibiotika und Neurohumorale Regulationen. By Dr. med. Ladislaus Mosonyi, Oberarzt at the II. Medizinischen Klinik der Universitat Budapest. Pp. 60; 13 ills. Jena: Gustav Fischer, 1959. Price DM 7.10.

This small booklet contains a general discussion of the results of some clinical and experimental studies of the neuro-humoral disturbances and other so-called side effects of antibiotics. The author concludes that they are caused by the same effects upon enzymatic activities which are responsible for their antibacterial effects. There is a list of 148 references. W.E.

The Influence of Hormones on Lipid Metabolism in Relation to Arteriosclerosis. By Abraham Dury and Carleton R.

UNIVERSITY OF MICHIGAN LIBRARIES

TREADWELL AND 35 OTHERS. Ann. New York Acad. Sci., Vol. 72, Art. 14. Pp. 267; illustrated. New York: New York Academy of Sciences, 1959. Price, $4.00.

THIS volume consists of a series of papers presented at a conference held by the New York Academy of Sciences on April 11 and 12, 1958. The discussions are basically oriented. The material is arranged in four major groups, namely, 1) Metabolism of Lipids; Biosynthesis, Absorption, Transport; 2) Pituitary and Adrenal Hormones: Lipids and Arteriosclerosis; 3) Gonadal, Thyroid and Pancreatic Hormones: Lipids and Arteriosclerosis; and 4) Endocrines and Ground Substance.

It is recommended to all who are directly or indirectly concerned with clinical or laboratory investigation in this important field. C.Z.

Services for Children with Epilepsy. Prepared by the COMMITTEE ON CHILD HEALTH OF THE AMERICAN PUBLIC HEALTH ASSOCIATION. Pp. 124. New York: The American Public Health Association, 1958. Price, $1.50.

THIS valuable pamphlet prepared for the guidance of public health personnel outlines the services available for children with epilepsy. Included are sections on "Concepts and Facts about Epilepsy," "Causes and Prevention," Diagnosis and Planning for Care," "Treatment and Management," as well as "Special Services and Facilities," "Organization of Community Resources" and "Research."

In the appendices are considerations of the medical classification of seizures and the drug treatment of epilepsy among others. A bibliography of 76 references is included.

All in all this is an excellent pamphlet which should have much wider circulation than just public health personnel. It should be of interest and even required reading for all epileptics and their families, not to mention nurses and physicians who contact even an occasional case of the disease. S.G.

Systemic Lupus Erythematosus. Edited by GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D. Pp. 84; 21 ills. and 1 color plate. New York: Grune & Stratton, Inc., 1959. Price, $3.75.

CURRENT information regarding systemic lupus erythematosus has been summarized in this small volume. Chapters deal successively with the pathology of systemic lupus erythematosus; the nature and pathogenetic significance of the L.E. cell phenomenon; the blood in systemic lupus erythematosus; the clinical features of the disease; the disease in childhood; and, finally, therapy.

The contributors are all members or former members of the New York Mt. Sinai Hospital Staff where much of the important knowledge concerning this disease originated. The present monograph summarizes well the views held by this capable group of workers. C.Z.

Prelogical Experience. BY EDWARD S. TAUBER, M.D. AND MAURICE R. GREEN, M.D., Chairman of the Faculty of the William Alanson White Institute, and Member of the Faculty of the William Alanson White Institute, respectively. Pp. 186. New York: Basic Books, Inc., 1959. Price, $3.75.

THE authors state their determination to explore the prelogical forms of thinking such as dreams, day-dreams, extra-sensory perceptions, hunches, and the like. This is needed because of their contention that not enough importance is attributed to them in current psychoanalytic theory or employed in actual psychoanalytic therapeutic technique. The avowed attempt is to demonstrate that such prelogical thinking processes have an extraordinarily important contribution to make to dream interpretation and analytic therapy. To those serious students of psychoanalytic psychology, the re-emphasis on such pre-verbal communication is redundant whereas the actual attempt is sketchy, incomplete and does not contribute much original or additional material. S.H.

Blood Groups. British Medical Bulletin, Vol. 15, No. 2, May, 1959. Pp. 85; illustrated. London: The British Council, 1959. Price, $3.25.

THE wide medical and biological ramifications of the various blood groups are considered in this symposium. Among the topics discussed are blood group antibodies; the inheritance of blood groups; the antiglobulin reaction; hemolytic disease of the newborn and its management; blood groups as related, respectively, to disease, natural selection, anthropology, and genetic linkage; the biochemistry of blood group substances; blood group substances in human tissues, and their absorption on to erythrocytes; animal and human blood groups; and, finally, hemagglutinins in seeds.

The presentations are concise and authoritative. This volume is recommended to immunohematologists and all others interested in these important substances. C.Z.

The Plasma Proteins: Clinical Significance. BY PAUL G. WEIL, M.D., PH.D., Royal Victoria Hospital, Montreal. Pp. 133; 2 ills. Philadelphia and Montreal: J. B. Lippincott Co., 1959. Price, $3.50.

THIS is a concise and well-written exposition on plasma proteins and their clinical significance. Included are discussions not only of albumin, globulin, and fibrinogen but also of the more recently discovered proteins of plasma.

Because of its emphasis on clinical aspects, this monograph should be of especial value to physicians, interns, and medical students. C.Z.

Neuropharmacology. Edited by HAROLD A. ABRAMSON, M.D., Biological Laboratory, Cold Spring Harbor. Fourth Conference. Pp. 268; 48 ills. New York: Josiah Macy, Jr. Foundation, 1959. Price, $5.00.

THE fourth volume of this series is up to the high standards of the previous ones. The various participants are all qualified to write authoritatively. The section on structure-action of mescaline and related compounds is especially rewarding. M.O.

Low-Fat Diet; Reasons, Rules, and Recipes. By R. L. SWANK, M.D., Professor of Neurology, University of Oregon Medical School, and AAGOT GRIMSGAARD, Research Associate, University of Oregon Medical School. Pp. 143. Eugene, Oregon: University of Oregon Books, 1959. Price, $2.50.

THE authors, in extolling the virtues of the low-fat diet, state that "it is only in modern times that our bodies have harbored so many degenerative diseases . . ." The history of fat consumption in various cultures is briefly reviewed to demonstrate that the high levels of fat in present-day diets may be the principal factor involved in degenerative ailments. It is claimed that people are generally healthier on a low-fat diet. Evidence is presented supporting the view that multiple sclerosis is benefited by a low-fat diet. In addition, the diets are recommended for treatment of vascular sclerosis and obesity. Suggestions are provided for careful adherence to this type of dietary program. The latter portion of the monograph is devoted to a wide variety of recipes of low fat content which should be useful for patients and physicians desiring this type of dietary restriction. C.S.

Axenic Culture of Invertebrate Metazoa: A Goal. By ELLSWORTH C. DOUGHERTY AND 35 OTHERS. (Ann. New York Acad. Sci., 77, Art. 2, pp. 25–406.) New York: New York Acad. Sci., 1959. Price, $4.50.

Germfree Vertebrates: Present Status. By JAMES A. REYNIERS AND 30 OTHERS. (Ann. New York Acad. Sci., 78, Art. 1, pp. 1–400.) New York: New York Acad. Sci., 1959. Price, $5.00.

World Directory of Venereal-Disease Treatment Centres at Ports. Pp. 162. Geneva: World Health Organization, 1959. Price, $1.75.

Der wissenschaftliche Rahmen der Homöopathie. Edited by DR. MED. W. SCHWARZHAUPT AND DR. MED. R. SEITSCHECK. Pp. 357; illustrated. Stuttgart: Hippokrates Verlag, 1959.

As stated in the subtitle, this is an excerpt of homeopathic thinking as portrayed in the speeches presented at the 22nd International Congress for Homeopathic Medicine held in Salzburg in 1958. R.K.

Smoking: The Cancer Controversy. By SIR RONALD A. FISHER, Sc.D., F.R.S. Pp. 47. Edinburgh: Oliver & Boyd, Ltd., 1959. Price, 2s. 6d.

Maximum Permissible Body Burdens and Maximum Permissible Concentrations of Radionuclides in Air and in Water for Occupational Exposure. National Bureau of Standards Handbook 69. Pp. 95. Washington: Superintendent of Documents, U.S. Government Printing Office, 1959. Price, $.35.

Die Behandlung der Magen- und Darmkrankheiten in der Praxis. By DR. MED. GUSTAV R. HEYER, DR. MED. WILHELM SCHWARZHAUPT AND DR. MED. WERNER TIEGEL. Pp. 203; 4 ills. Stuttgart: Hippokrates Verlag, 1959.

Physiology of Prematurity. Transactions of the Third Conference, March 25, 26, and 27, 1958, Princeton, New Jersey. Edited by JONATHAN T. LANMAN, M.D., New York University-Bellevue Medical Center. Pp. 157; 56 ills. New York: Josiah Macy, Jr. Foundation, 1959. Price, $3.00.

THIS reports the informal presentations and discussions of a group of experts on some of the frontiers of research in prematurity. The subjects discussed are: Metabolic and Enzymic Changes During Development; Bile Pigment Metabolism and Liver Function; Congenitally Jaundiced Rats; Glucuronic Acid in Treatment of Bilirubinemia; and Biochemical Mechanisms in Glucuronide Formation. I.W.

The Biology of the Amoeba. By HENRY I. HIRSHFIELD AND 22 OTHERS. Pp. 303; 239 ills. New York: New York Academy of Sciences, 1959. Price, $4.50.

AN impressive list of 23 competent researchers contributed to this excellent monograph, consisting of 20 articles covering various aspects of structure and taxonomy, physical studies, cell division, cytochemistry, enzymes, and nuclear-cytoplasmic relationships. The unusual large protozoan forms belonging to the Amoeba and Pelomyxa (Chaos) genera served as excellent tools for the authors' studies, which have provided important basic information in the field of cytokinesis, cytochemistry, and cytogenetics. Because this volume summarizes the active research done with the amebae during the past 20 years, it should be of great value to the cytochemist, geneticist, and parasitologist. A.L.

UNIVERSITY OF MICHIGAN LIBRARIES

A Short History of Psychotherapy in Theory and Practice. By Nigel Walker, Ph.D., Chairman, Davidson Clinic, Edinburgh. Pp. 185; 11 ills. New York: The Noonday Press, 1959. Price, $1.45.

This book aims at tracing the development of the technical differences between the various schools of psychotherapy. The author limits himself to discussion of theoretical disagreements connected with these technical differences.

The author uses Feudian psychoanalysis as the model, and attempts to trace the changes in theoretical understanding that occurred in analysis. The reader is led through the theoretical disagreements of Alfred Adler, Carl Rogers, Carl Jung, and the cultural school of psychoanalysts.

Aside from the psychotherapeutic techniques, all of which are descended from Freud, the author discusses suggestion and conditioning. The works of Emile Cone, and Pavlov are described. Group psychotherapy is described and an appendix on child psychotherapy and psychosomatic medicine is included. Each chapter is included with a list of books recommended for reading.

The author handles this difficult subject unusually well and with a great deal of objectivity. This book will interest the psychotherapist, and all persons interested in the subject. The book will appeal to the intelligent layman and student of psychology.

M.B.

Adaptation to Extrauterine Life. Report of the 31st Ross Conference on Pediatric Research. Edited by Thomas K. Oliver, Jr., M.D. Pp. 94; 25 ills. Columbus, Ohio: Ross Laboratories, 1959.

A Manual of Bandaging, Strapping and Splinting. By Augustus Thorndike, M.D., Harvard Medical School. 3rd ed. Pp. 148; 125 ills. Philadelphia: Lea & Febiger, 1959. Price, $2.75.

This little manual is perhaps best recommended for its semi-diagrammatic drawings which illustrate very well the method of applying various types of bandages, straps and splints. In certain instances it would seem that the text, which is very brief, strays somewhat from the subject matter implied by the title. This straying, however, only occurs in a few areas and does not detract from the manual. It is unfortunate, that in one or two diagrams, the author has left out the padding necessary for areas, such as the axilla, and since this manual is one that will be used by others than physicians, it perhaps is something that should be corrected.

R.T.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES
Published Monthly. Illustrated.
Subscription price: 1 year $10.00; 2 years $18.00.
(One year subscription to Canada, $10.50; all other countries $12.00)
All foreign subscriptions payable in advance in United States dollars.
Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

Manuscripts intended for publication in The American Journal of the Medical Sciences, and correspondence should be sent to the Editor:

Dr. Richard A. Kern, Temple University Hospital, Philadelphia 40, Pa.

Articles are accepted for publication in The American Journal of the Medical Sciences exclusively, except in the case of subsequent publication in Society proceedings.

Manuscripts should be typewritten on one side only, of good quality paper and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle.

Illustrations accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. Line drawings and charts should be prepared with black India ink. Special arrangements can be made for printing color plates, elaborate tables or an excessive number of illustrations.

References should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

Return Postage should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 Reprints will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100. An order form showing cost of reprints is sent with proof. Individual reprints can usually be obtained by writing directly to the author.